UNIVERSITY OF SYDNEY

FACULTY OF MEDICINE

IMMUNOMODULATORS IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

This thesis is submitted in fulfilment of the requirements for the degree of

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STATEMENT OF AUTHENTICATION

This thesis is submitted to the University of Sydney in fulfilment of the requirement for the degree of Doctor of Philosophy.

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Viraj Kariyawasam

26 August 2019

AUTHOR ATTRIBUTION STATEMENT

STUDY 1

RWL: study supervision. RWL, VCK, PHK: study concept; study design. RWL, VCK, DBJ, CM, GB, GC, JC, PCL, KM, RRW, TH, CPS, JA: patient recruitment, acquisition of data. RWL, VCK, JA, PHK, CPS: manuscript drafting, critical revision. RWL, VCK: statistical analysis, analysis and interpretation of data

STUDY 2

VK contributed to study design, data acquisition, analysis, and wrote and revised the manuscript. FM contributed to analysis and writing up of the manuscript. CS, PK, BJ, CM, GB, GC, JC, SP and JA contributed to data acquisition and manuscript revision. RL contributed to study design, manuscript revision and intellectual content.

STUDY 3

VCK and MGW contributed equally to study design, data acquisition, analysis, and wrote and revised the manuscript. PAB, KVP and RG contributed to data acquisition and manuscript revision. PMI and JDS contributed to study design, manuscript revision and intellectual content. All authors approved the final version of the manuscript.

STUDY 4

VK contributed to study design, data acquisition, analysis, and wrote and revised the manuscript. SK and FM contributed to analysis and writing up of the manuscript. CS, PK, BJ, CM, GB, GC, JC, PL, KM, RW, TH, JA and PP contributed to data acquisition and manuscript revision. RL contributed to study design, manuscript revision and intellectual content.

STUDY 5

VCK and WC contributed equally to study design, data acquisition, analysis, and wrote and revised the manuscript. SK, FM and HHS contributed to data acquisition and manuscript revision. MF, ND and RWL contributed to study design, manuscript revision and intellectual content. All authors approved the final version of the manuscript.

SUPERVISOR STATEMENT

As the supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct. I also hereby certify that all co-authors of the published or submitted papers agree to Viraj Kariyawasam submitting those papers as part of his Doctoral Thesis.

Professor Rupert Leong

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PUBLICATIONS AND PRESENTATIONS REALTED TO THIS THESIS

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Kariyawasam VC, Ward MG, Blaker PA, Patel KV, Goel R, Sanderson JD, et al. Thiopurines Dosed to a Therapeutic 6-Thioguanine Level in Combination with Adalimumab Are More Effective Than Subtherapeutic Thiopurine-based Combination Therapy or Adalimumab Monotherapy During Induction and Maintenance in Patients with Long-standing Crohn's Disease. Inflammatory Bowel Disease. 2017 Sep;23(9):1555–65.

Kariyawasam VC, Selinger CP, Katelaris PH, Jones DB, McDonald C, Barr G, et al. Early Use of Thiopurines or Methotrexate Reduces Major Abdominal and Perianal Surgery in Crohn's Disease. Inflammatory Bowel Dis. Oxford University Press; 2014 Aug 1;20(8):1382–90.

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Chan W, Kariyawasam VC, Kim S, Shim HH, Mourad FH, Ding N, Ferrante M, Leong RW. Gastroenterologists' Preference on the Use of Immunomodulators and Biological Therapies in Elderly Patients with Ulcerative Colitis – an International Survey – submitted to Alimentary Pharmacology and Therapeutics

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Kariyawasam VC, Wang RR, Middleton KL, Lunney PC, Selinger C, Collins GD, et al. The natural history of ulcerative colitis and predictors of the use of immunomodulators and colectomy: the Sydney Inflammatory Bowel Disease Cohort 1946-2012 - *Australian Gastroenterology week - Adelaide Convention Centre, Adelaide, Australia – 16-19 October 2012*

Kariyawasam VC, Wang RR, Middleton KL, Lunney PC, Selinger C, et al. Natural history of Elderly onset inflammatory bowel disease - Sydney IBD Cohort (1942-2012)- 8th Congress of European Crohn's and Colitis Association, Vienna, Australia – 14-16th February 2013.

Kariyawasam VC, Wang RR, Middleton KL, Lunney PC, Selinger C, Collins GD, et al. Early Treatment with Immunomodulators Is Associated With Change in the Natural History of Inflammatory Bowel Disease-Multi-centre Longitudinal Study-Sydney, Australia 1942-2012 – Digestive Disease Week, Orange Country Convention Center, Orlando, Florida, United States – 19-21 May 2013

Kariyawasam VC, Ward MG, Blaker PA, Anderson SH, Sanderson JD, Irving PM. Azathioprine decreases the risk of adalimumab primary non-response and secondary loss of response but only if adequately dosed - Digestive Disease Week, Hyatt Regency McCormic Place, Chicago, Illinois, United States – 3-6 May 2014

POSTER PRESENTATIONS

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Kariyawasam VC, Wang RR, Middleton KL, Lunney PC, Selinger C, Collins GD, at al. Natural history of Crohn's disease and changes in the use of immunomodulators over time: The Sydney Inflammatory Bowel Disease Cohort 1942-2012.- *Australian Gastroenterology week - Adelaide Convention Centre, Adelaide – 16-19 October 2012*

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ABBREVIATIONS

IM	Immunomodulators
TP	Thiopurines
IBD	Inflammatory bowel disease
CD	Crohn's disease
UC	Ulcerative colitis
HR	Hazard ratio
CI	Confidence interval
OR	Odds ratio
MP	Mercaptopurine
TG	Thioguanine
AZA	Azathioprine
TGN	Thioguanine nucleotide
TNF	Tumour Necrotic Factor
CRP	C-Reactive Protein
ADA	Anti-drug antibodies
MCV	Mean corpuscular volume

ABSTRACT

BACKGROUND

Immunomodulators (IM), mainly thiopurines (TP) have been used in the treatment of inflammatory bowel disease (IBD) for over 50 years. Over the last 20 years, the number of drugs available to treat IBD has grown. The role of IM cannot be understated as they alone may control IBD in the long term, and also improve the efficacy of biological agents when given as co-therapy. The newer therapies come at an exceptionally high financial cost, raising issues with affordability and cost effectiveness. Any evaluation of drug treatment needs to take into account the long-term outcomes, particular their efficacy in the reduction of major long-term morbidities related to chronic uncontrolled inflammation.

METHODS

Three retrospective cohort studies were conducted using the "Sydney IBD Cohort", updated in 2012, evaluating the surgical outcomes in patients with Crohn's disease (CD), Ulcerative colitis (UC) and elderly IBD patients. Fourth study was a retrospective, single-centre cohort study of patients with moderate-to-severe CD, assessing the influence of thiopurine on efficacy of adalimumab. Fifth, was a case-based survey conducted worldwide assessing gastroenterologists' selection of drug treatments based on patients' comorbidity and age in the management of moderate-to-severe UC.

RESULTS

Early IM was associated with significantly lower rates of initial abdominal surgery (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.35–0.69), recurrent abdominal surgery (HR, 0.44; 95% CI, 0.25–0.79) and perianal surgery (HR, 0.30; 95% CI, 0.16–0.56) in CD.

Early TP maintenance significantly decreased the need for colectomy (HR: 0.10, 95%CI: 0.03- 0.43) and proximal progression of disease extent (HR: 0.26, 95%CI: 0.10-0.78), after propensity score matching in UC.

TP dosed to therapeutic 6-thioguanine nucleotide levels (6-TGN) at induction were predictors of primary response (Odds ratio (OR): 4.32, 95% CI, 1.41–13.29) and time to failure (OR: 0.37 (0.15–0.89), and therapeutic 6-TGN in semesters were associated with remission semesters (OR 3.71, 95% CI, 1.87–7.34) in CD patients treated with adalimumab.

Charlson Comorbidity Index was associated with delayed IM introduction in CD (HR 0.863; 95% CI, 0.787–0.946) and UC (HR 0.807; 95% CI, 0.711–0.917) but not age. Early IM use was associated with reduced need for surgery in CD (HR 0.177; 95% CI, 0.089–0.351).

Comorbidity reduced the probability of prescribing IMs for elderly- (OR: 0.25, 95%CI: 0.16-0.38) and for younger-patients (OR: 0.56, 95%CI: 0.39-0.82) with UC. Conversely, elderly- and younger-patients with comorbidities were more likely to receive Vedolizumab (OR: 2.71, 95%CI: 1.98-3.71 and OR: 1.37, 95%CI: 1.01-1.86, respectively) and colectomy (OR: 5.40, 95%CI: 2.74-10.64 and OR: 4.46, 95%CI:2.25-8.87 respectively].

CONCLUSION

Early and sustained IM use is associated with reduced risk of surgery in CD patients in all age groups, including elderly. Similarly, early sustained TP maintenance is associated with reduced risk of colectomy and proximal disease progression in UC. TP dosed to therapeutic levels, improves the primary response and duration of activity of adalimumab. Comorbidity is the main factor influencing the use of IM in the elderly. The results of these studies affirm the position of immunomodulators, particularly thiopurines, in the current day treatment paradigm of IBD.

CHAPTER 1 : INTRODUCTION AND LITERATURE REVIEW

1.1 INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is an idiopathic, chronic, relapsing, inflammatory disorder of the intestinal tract caused by dysregulation of the immune response(1). It comprises Crohn's Disease (CD) and ulcerative colitis (UC), which differ in the anatomical location of involvement, pattern of inflammation and the layers of gut wall affected(2). CD involves the full thickness of the bowel wall and can involve any part of the gastrointestinal tract, although it most commonly affects the small bowel and/or large bowel whereas UC only affects the mucosal layer of the colon (2,3). UC extends proximally in a continuous manner starting from the anus whereas CD location may not be continuous (2,3). In the absence of treatment, both phenotypes cause chronic and permanent damage to the bowel leading to complications such as strictures, perforations, extra-intestinal manifestations and malignancies (4). Chronic uncontrolled inflammation in CD due to its transmural involvement leads to fistula and penetrating disease, which is not seen with UC (4). The aetiology of IBD is unclear, but involves environmental risk factors, probably acting via the intestinal microbiome, in a genetically susceptible individual leading to unconstrained immunological response against the intestinal wall (5).

The incidence and prevalence of IBD varies across different populations around the world (6). Historically, IBD was considered to be a disease of the developed world with highest incidences being reported in North America, Europe, Australia and New Zealand. There has been an increasing incidence in the recently-developed and developing countries (7-9).

Up to 80% of patients with CD present with an inflammatory phenotype and only 5% to 28% show a stricturing phenotype. However, around 50% develop stricturing and penetrating complications within 10 years of diagnosis, driven by intestinal damage and fibrosis due to uncontrolled inflammation(10). Stricturing disease may require surgical resection of the narrowed segment of the bowel.

Though treatment targets have changed over time, it still involves induction of remission followed by maintenance therapy. Clinical remission and objective markers of remission such as mucosal

healing are the current treatment targets (11). Chronic inflammation is associated with irreversible intestinal damage, increasing the risk of subsequent surgery (12).

Medical therapy includes corticosteroids, mesalazine (5-aminosalicylates) and immunomodulators (IMs) such as the thiopurines and methotrexate. However, since the approval of Infliximab in 1998 as the first biological agent to treat IBD, the number of drugs available to treat IBD has grown. These newer biological therapies, however, come at an exceptionally high financial cost, which is increasing exponentially with time. A recent Australian study found the total cost for anti-tumour necrotic factor (TNF) over the 7-year period was $380 million, with Infliximab prescription increasing fourfold over the study period, while Adalimumab increased by 6-fold(13). With increasing incidence of IBD in both developed and developing countries, affordability and cost effectiveness of biologic therapies needs to be critically evaluated, as a patient on biologic therapy will attract a higher treatment cost to the health care system, compared to a patient on IM therapy (14). However, multiple studies addressing the cost-benefit aspects of biologic therapies, have shown the significant savings gained by reducing disease complications, hospitalisations and surgery to be superior compared to the direct cost of the biologics (14). Similarly, due to its very low direct cost, if IMs are shown to reduce disease complications, hospitalizations and surgery, it will continue to be an attractive treatment option in both CD and UC. Biological agents are also associated with primary non-response, secondary loss of response, intolerances and side effects.

The role of IMs, therefore, cannot be understated. They alone may control IBD in the long term, and also improve the efficacy of biological agents when given as co-therapy. Any evaluation of drug treatment also needs to take into account the long-term outcomes, particular their efficacy in the reduction of major long-term morbidities such as major abdominal surgery and perianal surgery related to chronic uncontrolled inflammation.

1.2 Immunomodulators

1.2.1 Thiopurines

George Hitchings and Gertrude Elion recognized that by substituting sulfur at the 6 position of the purine bases with oxygen, led to the inhibition of purine utilization, cell cycle arrest and apoptosis. Their research led to the discovery of Mercaptopurine (MP) and Thioguanine (TG) in the 1940s **(15,16)**. In 1957, they discovered Azathioprine (AZA), 1 1-methyl-4-nitro-5-imidazolyl a derivative of MP. These drugs are commonly known as thiopurine analogues and were initially used for the treatment of childhood leukaemia, for which they received the Nobel prize in 1988**(16)**.

The first case series of using thiopurines for the treatment of UC and CD was published in the 1960s **(17,18)**. In 1980 George Present et al published the seminal paper demonstrating the effectiveness of thiopurines for the induction of remission in CD**(19)**. Even 60 years after its initial use in the treatment of IBD, there are still unanswered questions regarding the efficacy and safety of these drugs**(20)**.

1.2.2 METHOTREXATE

Although thiopurines are the first line IM in IBD, some patients may fail treatment or not tolerate treatment. As such a non-thiopurine second line agent needs to be available. Methotrexate, a folate antagonist reported by Sidney Farber in 1948, was first used in the treatment of childhood leukaemia. Since then, methotrexate has been used as an IM that is effective in treating a number of inflammatory disorders including IBD.

Kozarak et al first reported on the efficacy of methotrexate in a non-randomised open label induction study of 12 weeks duration. Since then several uncontrolled and controlled studies have shown benefits in CD. However, a recent Cochrane review did not find any evidence of support the use of methotrexate for the maintenance of remission in UC(21).

1.3 USE AND EFFICACY IN CROHN'S DISEASE

Surgery is one of the most objective outcome measures of treatment failure, since it is only performed if medication is not effective or tolerated and represents a hard endpoint in assessing the treatment efficacy in IBD. Surgical resection rates in published studies have varied widely, ranging between 24% to 61% in the first five years in CD (22). Despite several studies showing no change in CD intestinal resection rates, many others have shown a gradual decline over time (22-29). A recent metanalysis of population-based studies also identified a gradual decline in surgical rates over the last 6 decades, which has preceded the wide spread use of biologics (30). This reduction in surgical rates may also represent a change in the natural history of CD. However, most natural history studies are unable to demonstrate a positive impact of IMs, possibly due to their use in more severe disease, late introduction after development of strictures or fistulas, or insufficient patient follow-up.

1.3.1 Reducing intestinal surgery in Crohn's disease.

Ramdas et al studied a population-based cohort from Cardiff, UK, comprising of 341 CD patients diagnosed between 1986-2003. They first explored the impact of increasing use of early thiopurines on the surgical rates in adults. Thiopurine therapy within the first year of diagnosis increased from 3% in the earlier cohort to 25% in the most recent cohort (<0.0001). Corresponding intestinal resection rates at 5 years reduced from 59% to 25% respectively. In a multivariate cox regression analysis, early thiopurine use within the first year of diagnosis (HR: 0.47, 95%CI: 0.27-0.79), year of diagnosis ($HR_{early\ cohorts}$: 1.71, 95% CI: 1.1-2.5), disease location and early corticosteroid use were independently associated with intestinal surgery. The year of diagnosis being identified as an independent predictor raises the possibility that other significant factors (such patient management paradigms during that era, surgical approach, access to diagnostic tests) may have contributed towards this change in surgical rates.

Lakatos et al, also showed similar trends with early use of IMs, in a Hungarian cohort of 506 CD patients diagnosed between 1977-2009 (29). Early IM use within 5 years of diagnosis increased

from 6.2% to 46.2% over time. They found early use of azathioprine to be associated with reduced need for surgery, independent of the decade of diagnosis after using strict definitions and propensity score matching (HR; 0.42, 95% CI: 0.26-0.67) **(29)**. This study, therefore, suggested that thiopurines may successfully modify the natural history of IBD and reduce the need for surgery.

Two recent prospective randomised controlled studies failed to demonstrate efficacy of early thiopurines in the management of CD **(31,32)**. Both of these studies had a number of deficiencies. The sample sizes were small, follow up periods were too brief ranging from 1.5 to 3 years, the outcomes were subjective, and the control subjects eventually required commencement of thiopurines which may have negated any benefit. In addition, most studies have only focused on the short-term outcomes of thiopurine therapy, which are recognised to cause side effects or intolerance in up to 40% patients, that can lead to a negative result **(33).** Higher dosing at 2.5mg/kg in both these studies, may have also led to poor tolerance and reduced adherence, as most side effects of thiopurines are dose dependent**(34)**. With use of short-term subjective outcomes as end points rather than surgery and weight-based dosing without therapeutic drug monitoring (TDM), the authors may have underestimated the effectiveness of therapy. It is known that concentration of 6-thioguanine nucleotide (6-TGN) is associated with the therapeutic response **(35)**.

There are no population based long term studies evaluating the efficacy of Methotrexate in reducing surgical rates in CD. IM therapy in CD often involves thiopurines as first-line therapy and methotrexate is only used as second-line treatment after failure of thiopurines **(36).** Therefore, to demonstrate the effectiveness of the early IM strategy on surgical outcomes, it requires a study that includes patients who are treated with thiopurines, as well as those who were started on methotrexate due to thiopurine intolerance or failure. Few studies have evaluated the IM strategy using well-described IBD cohorts with sufficient patient-years of follow up to demonstrate whether the need for CD surgery diminishes.

1.3.2 PREVENTION OF SURGICAL RECURRENCE AFTER INTESTINAL RESECTION

Given the nature of CD, surgery is not curative and post-operative recurrence is common. Clinical and endoscopic recurrence one-year post surgery can be as high as 10-38% and 35-85% respectively **(37)**. A recent meta-analysis of population-based studies found the overall risk of a

second intestinal resection to be 28.7%; with 5 and 10-year risk being 24.2% and 35% respectively (38). Frokllis et al, also found a significant reduction in the 10-year risk of a second surgery pre and post 1980: 44.6% pre versus 33.2% post 1980. Most of the studies included in this metanalysis predated the widespread use of biologics. (38).

Peyrin-Biroulet et al in a recent meta-analysis demonstrated the efficacy of thiopurine analogues in reducing clinical and endoscopic post-operative recurrence (39). However, population-based studies have yet to confirm this benefit (23). Papay et al exploring the benefits of thiopurines in preventing surgical recurrence among 326 patients who had an intestinal resection, identified that maintaining thiopurines for at least 36 months significantly reduced surgical recurrence (HR: 0.41, 95% CI: 0.23-0.76) (40). However, the study can be criticised for not addressing the immortal time bias favouring azathioprine, which may have contributed towards the positive findings.

1.4 USE AND EFFICACY IN ULCERATIVE COLITIS

Chronic relapsing and remitting inflammation causing intestinal damage and fibrosis is associated with increased risk of surgery in UC (12). As surgery is an objectively identifiable and clinically important event in the natural history of UC, it makes for an attractive clinical endpoint, particularly when evaluating the efficacy of therapy.

The Stockholm county cohort of patients diagnosed between 1966-1984 had cumulative colectomy rates of 20%, 28% and 45% at 5, 10 and 25 years after diagnosis respectively (41). However, subsequent studies have consistently reported lower rates of colectomy at 1, 5 and 10 years after diagnosis ranging from 0.5%-6%, 3%-13% and 8.5%-19% respectively (27,42-48). A recent population-based cohort study from Australia reported similar colectomy rates of 15% at 10 years and 31% at 30 years (49). The decline in colectomy rates occurred prior to biological agents becoming widely available. Therefore, the increasing and earlier use of thiopurines over time, may be responsible for the reduced need for colectomy.

1.4.1 REDUCING THE RISK OF COLECTOMY IN ULCERATIVE COLITIS

A recent Cochrane review strongly favoured thiopurines for maintaining clinical remission, but lacked high-quality evidence **(50)**. Colectomy was not assessed as a clinical endpoint in this review.

A number of population-based studies have tried to evaluate the impact of thiopurine maintenance on the risk of colectomy, with limited success. Most studies have shown a significant increase in the use of thiopurines over time, with an associated reduction in surgical rates. However, they failed to demonstrate a consistent association between the two events **(51-58)**.

A Canadian population-based study from Manitoba including 3,752 UC patients demonstrated a significant reduction in colectomy rates at 2 years among patients who were maintained on thiopurines for a minimum of 16 weeks (5.6% vs 12.8%)**(51)**. A large Danish registry study comprising 35,783 patients diagnosed between 1979 and 2011, failed to indicate any protective effect of thiopurine exposure on colectomy **(52)**. Given the nature of the study, data was not available on the disease severity at diagnosis, smoking status and also lacked evidence on medication maintenance and adherence.

A population-based study from the United Kingdom of incident cases of UC, diagnosed between 1989- 2009, found maintenance of thiopurines for more than 12 months to be associated with a 71% reduction in risk of surgery (HR: 0.29, 95%CI: 0.210.40) **(53)**. However, early thiopurine use, defined as introduction of thiopurines within 1 year of diagnosis of UC, did not reduce surgical rates. This may be attributed to some patients with early onset of severe disease requiring thiopurines, being either refractory to therapy or having had insufficient time to benefit from thiopurines before surgery. Similar to other registry studies it lacked data on disease extent and severity. CañasVentura et al described an increased risk of colectomy at 5 years in patients receiving thiopurine therapy within first 33 months of diagnosis vs those started after this period (HR = 4.9, 95%CI: 3.2-7.8) **(54)**.

Most of these studies failed to address the possible confounders associated with early thiopurine use. None of the studies used matching on propensity scores, a technique commonly used to control for measured confounders in observational studies(55). They also lacked a strict definition for thiopurine maintenance to ensure adequate exposure prior to surgery, considering the lengthy median time to response associated with thiopurines before deeming therapy to be futile (56-58).

Evidence for the efficacy of methotrexate on maintenance of remission in UC is disappointing. A recent Cochrane review failed to demonstrate any benefit of methotrexate in the treatment of UC (21). There is no long-term population-based data on the colectomy rates, due to its limited use in UC as compared to CD.

1.4.2 Reducing the proximal progression in disease in ulcerative colitis

Disease extent in UC is dynamic, with 27% to 54% of patients who were initially diagnosed with proctitis or left-sided colitis progressing to more extensive involvement over time(27). Rate of progression from proctitis to left-sided colitis was 28%–30%, and to extensive colitis was 14%–16%; from left-sided colitis to extensive colitis was 21%–34% (59). The 5 and 10 year risk of progression of disease was 17.8% (95% CI: 12.3-25.1) and 31% (95% CI: 23.5-39.7) respectively(59).

Proximal disease extension appears to be a marker of severe disease, not only because it is associated with higher disease burden and therapeutic requirements, but also as it has been shown to be associated with higher rates of colectomy(27). These patients also had a higher need for biologics, more active disease and increased hospitalisations compared to controls who started with extensive colitis(60).

Diagnosis at a young age, extra-intestinal manifestations, refractory disease and never-smoking status have all been associated with an increased risk of disease progression, though these findings have been inconsistent (59).

This raises the question of whether earlier treatment of active disease can prevent disease progression. However, there are no studies looking at the impact of different therapeutic options on the risk of progression of disease in UC.

1.5 USE AND EFFICACY WITH BIOLOGICS

Since the approval of infliximab in 1998, anti-TNF antibodies (infliximab, adalimumab, certolizumab and golimumab) have revolutionized the management of IBD. Despite having an early clinical response rate of around 60-70%, up to 50% of those who responded initially will develop loss of response over time. Following loss of response, subsequent primary non-response to other biological agents increase, suggesting that exposure to anti-TNF agents might modify inflammatory pathways and increase resistance to second- and third-line biological agents (61,62). Up until the recent approval of vedolizumab and golimumab for UC and ustekinumab for CD, infliximab and adalimumab were the only anti TNF drugs licensed to treat IBD in Australia**(13)**. It is therefore desirable to optimise the use of each anti TNF drug to avoid treatment failure and preserve treatment efficacy for as long as possible. Hence, it is crucial to identify any modifiable factors that are associated with response and loss of response to improve outcomes.

1.5.1 IMPROVING PRIMARY RESPONSE

Primary non-response to anti TNF should not be assessed before week 8-12 in both CD and UC as successful remission induction can be still accrued after 3 infliximab infusions at 0,2 and 6 weeks and 3-5 bi weekly adalimumab injections. The reported primary non response rates in CD and UC are around 20-40% in clinical trials with both infliximab and adalimumab; with lower rates of 10-20% in clinical 'real life' series **(61,63)**.

Several factors have been identified to be associated with an increased risk of primary non-response in CD. In patients treated with infliximab, longer disease duration, small bowel involvement, smoking and normal C-reactive protein (CRP) were associated with increased risk of primary non-response (64). A randomised controlled study looking at the benefits of early IM therapy started at day 0 with the first infusion of infliximab, found a greater proportion of patients in clinical remission at week 14 and up to week 52 (65). A recent meta-analysis of patient level data in the biological registration trials also confirmed this finding, showing increased odds of response at week 4-14 (OR, 2.02; 95% CI, 1.09–3.72) with the concomitant use of IMs (66).

However, the evidence to support combination therapy with adalimumab is sparse. The same meta-analysis that showed benefit of concomitant IM therapy with infliximab, did not find similar association with adalimumab (OR 0.88, 95% CI, 0.58–1.35) (66). A recent prospective study randomizing treatment-naive patients with moderate-to-severe CD to either adalimumab monotherapy or combination therapy with thiopurines started at day 0, did not find a difference in response rate at week 12 (67). Subgroup-analysis of patients on thiopurines, found no difference in response based on 6-TGN levels being >250pmol/8x10^8 RBCs(67).

Conversely, a recent meta-analysis and a 'real life' series of patient data found adalimumab monotherapy to be slightly inferior to combination therapy for induction of remission (OR: 0.78, 95% CI: 0.64–0.96, P=0.02) (68). In another recent study, Ungar et al found significantly higher proportion of ADAs in primary non-responders to adalimumab, developing as early as 2 weeks (64% vs 25%). This raises the question of whether therapeutic levels of thiopurines are required prior to starting adalimumab to improve primary response rates (69). The benefits of pre-treatment IMs in reducing ADAs have been previously shown in murine models(70). This may be even more relevant given the slow median time to response (3.1 months) for thiopurines(19). In the meta-analysis by Koplyv et al biologics being started in a proportion of patients who failed IMs, which were continued, may have contributed towards the positive findings supporting combination therapy (68).

1.5.2 REDUCING SECONDARY LOSS OF RESPONSE

An European Crohn's and Colitis Organisation workshop recently defined loss of response as re-emergence of clinical symptoms, and/or objective measures of inflammation(71). However, some authors have defined loss of response as need for anti-TNF dose intensification, and others as anti TNF caseation and/or surgery(72,73). Lack of uniformity in definitions and consensus make it difficult to estimate the real magnitude of secondary loss of response.

Based on the need for dose intensification, two meta-analyses estimated the annual risk for loss of response after first 12 months to be 13% for infliximab and as high as 24% for adalimumab across CD trials and clinical case-series (72,74). The mean percentage of loss of response across all studies was 37% for both infliximab and adalimumab, with no difference found between the fully humanized adalimumab and chimeric IgG infliximab.

Development of anti-drug antibodies(ADAs) is associated with secondary loss of response with both infliximab and adalimumab **(72,74)**. Male gender, smoking, family history of IBD, colonic disease, presence of extra-intestinal manifestations, low dose induction therapy, long disease duration, higher initial disease activity, lack of deep remission at week 12, previous treatment with anti TNF and previous primary non-response to infliximab were identified as predictors of secondary loss of response to adalimumab **(74,75)**.

Concomitant IM therapy with infliximab has been shown to be associated with a significant reduction in the proportion of patients testing positive for ADA **(72)**. Both SONIC and SUCCESS trials demonstrated higher rates of clinical remission in patients treated with combination therapy as compared to either treatment alone at 6 and 12 months in patients with CD and UC**(76,77)**.

Unlike with infliximab, concomitant IM therapy with adalimumab was not identified to reduce the development of ADAs nor was it useful in preventing loss of response(74). Even though there was

no benefit of concomitant therapy in achieving clinical remission at 26 weeks, Matsumoto et al found significantly higher rate of endoscopic improvement in the combination group compared to adalimumab monotherapy respectively (84.2% vs 63.9%)(67).

It is unclear if continuing combination therapy long term adds benefit to regular scheduled dosing of infliximab(72). Sokol et al found significantly lower clinical relapses and perianal complications in patients maintained on combination therapy(78). The maximal CRP and the dose of infliximab used was lower in patients who continued combination therapy(78). A recent study evaluating three strategies of reducing the dose of thiopurines versus maintaining treatment dosing versus withdrawing completely, all in combination with Infliximab, found reducing the dose had similar benefits to maintaining the full dose(79). Another recent Cochrane review failed to arrive at a conclusion with regard to withdrawing IM therapy when used as combination therapy with biologics due to lack of evidence(80). Irrespective of the published literature, the common practice within the gastroenterologist community was to stop IM in patients who were in clinical remission after commencing anti TNF, especially with adalimumab. It is not known whether this practice is safer in reducing the potential for adverse effects such as infections and malignancies or increases the risk of loss of response to the anti TNF.

1.5.3 THIOPURINE DRUG MONITORING TO IMPROVE OUTCOME

The correlation between thiopurine metabolite levels and clinical response has been extensively investigated and confirmed in a recent meta-analysis(81). The pooled odds ratio for clinical remission among patients who achieved a 6-thiogunanine nucleotide level over 230 and 260 pmol/8.10^8 RBC was 3.15 (95% CI 2.41-4.11) compared to those with lower levels (81).

Data is emerging demonstrating the intensity of concomitant immunomodulation influences the pharmacokinetics of anti TNF therapy and clinical response. It has been shown, that methotrexate reduced immunogenicity to infliximab in a dose dependent manner, with odds of developing

ADAs reducing from 0.36 (95%CI 0.18-0.74) in the 5-10mg/week dose to 0.14 (95% CI 0.07-0.28) in the 22.5 mg/week, relative to patients not treated with methotrexate**(82)**.

Bouguen et al, in a post hoc analysis of SONIC trial, evaluated if the difference in mean corpuscular volume of red blood cells (MCV; difference between pre- and post-treatment MCV) of 7 femtoliters may be a surrogate marker of therapeutic 6-TGN levels. The authors assessed this MCV change on mucosal healing and maintaining therapeutic infliximab levels**(83)**. Mucosal healing was achieved in 75% in patients with a delta MCV of > 7, compared to 47.1% in patients who had a delta MCV of <7 (p=0.0172) **(83)**. Steroid free remission rates were 77.9% versus 64.4% (p=0.015) in the two groups **(83)**. The odds of achieving mucosal healing at week 26 was significantly higher in the patients achieving delta MCV >7 (OR: 3.86, 95%CI: 1.05-14.18, p=0.042) **(83)**. They also demonstrated that the percentage of patients with trough levels of infliximab above 3 mg/mL to be significantly higher in patients with a delta MCV >7 (68.4% versus 38.8%; P=0032) **(83)**. This was the first study to demonstrate that lower 6-TGN levels might be less effective in combination therapy, using delta MCV as a surrogate maker of therapeutic levels of 6-TGN. Unfortunately, measurement of 6-TGN was not performed in the SONIC trial.

In a cross sectional study assessing the correlation between 6-TGN levels and infliximab trough levels, a 6-TGN level of ≥125 pmol/8.10^8 RBC best-predicted for higher infliximab levels (area under receiver operating characteristic, 0.86; p<0.001) **(84)**. Patients in the lowest 6-TGN quartile had infliximab levels similar to patients not on thiopurines, 4.3 vs 4.8mcg/mL respectively (p=0.8) **(84)**. Patients with 6-TGN levels <125 pmol/8.10^8 RBC were more likely to develop ADAs (OR: 13, 95%CI: 2.4-72.5, p=0.01)**(84).**

Similarly, in a recent open label, prospective, randomised clinical trial assessing the optimal azathioprine dose required to improve efficacy in combination with infliximab, a level of 105 pmol/8.10^8 RBC (Likelihood ratio 7.67; Sensitivity=67%, specificity=92%) was identified as the optimal cut off to predict for optimal infliximab pharmacokinetics**(79)**.

Currently available evidence is conflicting regarding the benefit of concomitant IM therapy with adalimumab in improving clinical outcomes or adalimumab pharmacokinetics **(74,85)**. No studies

have evaluated the optimal dose of thiopurine, based on 6-TGN levels, needed to improve clinical outcomes in patients treated with thiopurines.

1.6 USE AND EFFICACY IN ELDERLY

The increase in the elderly population and rising incidence of IBD across all age groups are contributing towards the increasing prevalence of elderly IBD patients (86). It is estimated that around 25-35% of IBD patients are over the age of 60 years, with 10-15% diagnosed after the age of 60 (87,88). Disease onset after the age of 60 years is widely accepted as the definition of elderly onset IBD (86).

Currently, there are no age-specific treatment guidelines for elderly-onset IBD patients (86). Due to the differences in the disease progression, treatment efficacy and possible side effects, the current management practices designed for younger adult patients may not be applicable to the elderly (89). Presence of comorbidity and polypharmacy in elderly patients further underpins the challenges associated with managing this population at risk of opportunistic infections and cancers (90,91). It is also difficult to extract data for elderly IBD patients from clinical studies, as elderly and patients with comorbidity are often excluded from clinical trials(92).

Elderly patients with UC, but not patients with CD, have higher risk of IBD-related hospitalization compared to younger patients (88,93,94). Elderly CD patients have higher risk of surgery at or shortly after diagnosis, but long-term surgery risk appeared to be similar to younger onset disease(94,95). More recent studies have all demonstrated higher surgery rates in elderly onset UC, compared to younger onset patients (96,97). Elderly patients with IBD have significantly higher post-operative morbidity and mortality, compared to younger onset IBD patients, highlighting the need to optimise management in these patients (93,98,99).

Based on these risks and benefits, recent "European Crohn's and Colitis Organisation Topical Review on IBD in the Elderly" recommends that clinicians to assess an individual's frailty rather than only considering an individual's chronological/biological age when making management decisions (86).

1.6.1 *USE AND FACTORS INFLUENCING ITS USE IN ELDERLY*

Studies have constantly shown lower use of IMs in elderly IBD patients compared to younger IBD patients(88,95,97,100-102).

Lakatos et al reported a significantly lower azathioprine use in elderly onset CD patients (28.6%) compared to younger onset CD patients (42.6%), in a cohort of patients diagnosed between 1977-2008(95). They found similar differences in UC patients(95). Similar findings were observed in a recent Spanish study, which reported a cumulative probability of starting on immunosuppressants of 15% and 36% in elderly onset and 27% and 53% in adult-onset UC patients at 1 and 5 years respectively ($p<0.0001$) (97). Similarly, the rate in CD was 28% and 57% in elderly onset and 48% and 80% in adult-onset patients at 1 and 5 years respectively ($p<0.0001$) (97).

There appears to be a high steroid dependence, as reported by Juneja et al, in a study of 400 elderly IBD patients, where 32% were receiving maintenance corticosteroids(103). Despite high rate of steroid dependency, thiopurines and methotrexate were used in only 6% and 1% of patients, respectively(103). Despite having an increased risk of hospitalisation, surgery, post-surgical complications and steroid dependency, IMs are being underutilized in the elderly onset IBD patients(93,94,96,99).

No differences in efficacy or potential adverse events, have been noted with the use of thiopurines, based on age(104), raising the possibility of other factors influencing the use of IMs in elderly. One of the major determinants would be the documented increased risk of malignancy. Patients aged $\geq$65 receiving thiopurines were found to be 2.6 times more likely to develop lymphoma than their younger counterparts(105). The crude incidence rate of non-melanoma skin

cancer was 0.84/100 and 5.70/100 patient years for patients over the age of 65, who have never used and currently receiving thiopurines(106). Similar findings were noted in a US population-based study, but found the increased risk reducing to pre-exposure levels after stopping thiopurines(107).

A recently published large European population-based study identified older age at diagnosis (HR: 1.05, 95%CI 1.04-1.06) and smoking (HR: 1.4, 95%CI: 1.12-1.76) as factors associated with increased risk of extracolonic cancer (108). However, the use of IMs were not associated with increased risk in this population (108). A study from France, reported similar risk of intestinal cancer in elderly IBD patients and aged matched general population (109).

Older age is known to be associated with polypharmacy and increased comorbidities in elderly IBD patients, similar to the general population (110). Parian et al. in a cohort study of 190 elderly IBD patients, described the increased reliance on steroids associated with polypharmacy. Despite the uncertain efficacy of mesalazine for CD (111), 70% of the elderly patients with CD were on mesalazine maintenance therapy, including 71% of CD patients with moderate to severe disease. However, they did not assess if these decisions were impacted by polypharmacy, age or comorbidities.

Polypharmacy in elderly may indicate higher rates of comorbidities, frailty and potential for drug interactions. In these scenarios, treating physician may consider avoiding medications like IMs, due to potential drug interactions and side effects. Contrary to what is expected Fries et al, reported an increased likelihood of IM use in patients with polypharmacy (112).

The knowledge and attitude towards IM prescription by the treating physician has never been assessed. Patients' age, lack of clear evidence for drug efficacy in the elderly population, underestimating the increased mortality risk, hospitalization, morbidity associated poorly treated IBD and concerns about drug side effects, may influence their decision-making process.

1.6.2 *Reducing the risk of surgery in elderly IBD*

Elderly onset IBD was reported to be a milder form of the disease compared to younger onset, with low risk of surgery across both CD (28.6% versus 33.8% respectively) and UC (1.9% versus 4.1% respectively) (95). In a recent meta-analysis, elderly onset IBD patients were found to have similar risk of surgical intervention (OR: 0.70, 95%CI: 0.40-1.22) compared to younger onset patients (113). However, in contrast, elderly onset UC patients were significantly more likely to undergo surgery (OR: 1.36, 95% CI: 1.18-1.57, p<0.001) (113). More recent population cohort studies described similarly increased rates of colectomy, in elderly IBD patients(97).

A recent large registry study from Sweden again demonstrated a higher surgery rate among all elderly patients compared to adults (13% versus 10% respectively) (101). Despite the increase risk of surgery, the cumulative use of IMs at 5 years was lower in the elderly patients compared to other younger onset (33% elderly CD patients versus 54% adults and 17% elderly UC patients versus 28% adults after 5 years) (101).

Charpentier et al, assessing the impact of IM use on the risk of surgery found no association in either CD or UC(100). In a recent study using the Clinical Practice Research Datalink in the UK, demonstrated a 70% reduction in the risk of colectomy (HR: 0.30, 95%CI: 0.15–0.58) in elderly onset UC patients, who were maintained on thiopurines for more than 12 months.(114). Thiopurine maintenance was not associated with surgical risk (114). Overall, the lack of evidence to support the use of IM in the elderly may be a contributing factor to its limited use in this age group.

1.7 Purpose of the thesis

There are number of gaps in the literature defining the role of role of immunomodulators in the contemporary treatment of IBD. With increasing healthcare cost related to management of IBD, associated with increasing incidence and cost related to biologics, affordability and cost effectiveness of treatment options need to be critically evaluated.

In this context, the overall aim of the current thesis is to investigate the long-term efficacy and use of immunomodulators, particularly thiopurines, in the current day treatment algorithm of IBD by:

- Investigating the influence of early immunomodulator strategy, on the long-term surgical outcomes of CD; initial abdominal surgery, recurrent abdominal surgery and perianal surgery.
- Investigate the impact of early thiopurine therapy on the risk of colectomy and proximal disease progression in UC
- Investigate the use of thiopurines in improving clinical outcomes of biologics, particularly adalimumab when used in combination.
- Identify the factors associated with the use of immunomodulators in elderly and the influence of early treatment on surgical outcome
- Identify the factors influencing the prescribing patterns of physicians treating elderly IBD.

The following hypothesis and research questions will be addressed throughout the thesis.

1.7.1 HYPOTHESIS AND AIMS

HYPOTHESIS 1:

- Early IM use, comprising either thiopurines or methotrexate for unsuccessful thiopurine usage, reduces initial and recurrent surgical rates in CD
- Aims:
  - The primary outcome measure was the cumulative probability of major abdominal surgery for CD stratified by early IM use.
  - The secondary outcome was the impact of early IM use on requirement for recurrent major abdominal surgery and perianal surgery.

HYPOTHESIS 2:

- Early use of Thiopurine reduces the rate of colectomy in patients with UC
- Aims:
  - The primary outcome measurement was the cumulative probability of colectomy in UC stratified by early thiopurine use.
  - The secondary outcome was to assess the impact of early thiopurine use on proximal progression of disease.

HYPOTHESIS 3:

- Concomitant use thiopurines, dosed to therapeutic levels, improves clinical responses and time to failure of adalimumab
- Aims:
  - Primary aim was to investigate the influence of concomitant immunomodulator therapy on clinical outcomes in Crohn's disease patients treated with ADA.
  - Secondary outcome was to assess whether therapeutic TGN concentrations were associated with improved outcomes compared with subtherapeutic TGNs in patients on thiopurine combination therapy.

HYPOTHESIS 4:

- Patients with elderly -onset IBD were less likely to receive IMs for IBD and that the decision to avoid IMs is driven by age
- Aim:
  - The primary was to compare IMs prescription rates between elderly-onset and younger IBD patients with a view to identifying patients characteristics

and clinical markers at presentation that predict the initiation of IMs therapy.

- The secondary outcome was the impact of early IMs use on the requirement of first surgery due to IBD.

HYPOTHESIS 5:

- Gastroenterologists' decision to prescribe medical treatment or recommend colectomy in elderly UC patients is driven by age and not comorbidity.
- Aim:
  - Primary aim was to assess gastroenterologists' decision to prescribe medical treatment versus colectomy in elderly UC patients, and identify the factors associated with their choices using logistic regression analysis.
  - Secondary aims were to identify conditions that preclude gastroenterologists from prescribing immunomodulators and biological agents, and whether patient age is considered a limitation to prescribing these medication classes.

CHAPTER 2 : (STUDY 1) IMPACT OF EARLY IM USE, COMPRISING EITHER THIOPURINES OR METHOTREXATE FOR UNSUCCESSFUL THIOPURINE USAGE, ON INITIAL AND RECURRENT SURGICAL RATES IN CROHN'S DISEASE

The content of this chapter is presented as a published study "Early Use of Thiopurines or Methotrexate Reduces Major Abdominal and Perianal Surgery in Crohn's Disease" in manuscript format.

Early Use of Thiopurines or Methotrexate Reduces Major Abdominal and Perianal Surgery in Crohn's Disease

(Short title: Early Immunomodulator therapy in Crohn's Disease)

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Abbreviations:

IM:	Immunomodulator
CD:	Crohn's Disease
HR:	Hazard Rate
CI:	Confidence Interval
Anti-TNF:	Anti-Tumor Necrosis Factor alpha
5-ASA:	5 Amino-salicylates
IQR:	Inter-Quartile Ranges
NNT:	Number Needed to Treat

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Author contributions

RWL: study supervision. RWL, VCK, PHK: study concept; study design. RWL, VCK, DBJ, CM, GB, GC, JC, PCL, KM, RRW, TH, CPS, JA: patient recruitment, acquisition of data. RWL, VCK, JA, PHK, CPS: manuscript drafting, critical revision. RWL, VCK: statistical analysis, analysis and interpretation of data

2.1 Abstract

Background

Earlier introduction of immunomodulators (IM) thiopurine or methotrexate is advocated to improve Crohn's disease (CD) outcomes but whether abdominal surgery can be prevented remains controversial.

Methods

A specialist-referred cohort of CD was recruited from 1970 to 2009. Early IM use was defined as commencement of azathioprine or methotrexate within 3-years of CD diagnosis and adherence of at least 6-months. Propensity score matching was conducted to correct for confounders influencing early IM introduction. Outcomes of interest were rates of initial and recurrent major abdominal surgery for CD and their predictive factors.

Results

A total of 1,035 consecutive CD patients (13,061 patient-years) were recruited. The risk of first and recurrent major abdominal surgery at 1, 5 and 10-years were 17.5%, 28.4% and 39.5%, and 5.9%, 19.0% and 33.3% respectively. Early IM use increased over time from 1.3% to 55.3% (P<0.0001) and was a significant independent predictor of lower rates of initial abdominal surgery (hazard ratio [HR]: 0.45, 95% confidence interval [CI]: 0.35-0.69), recurrent abdominal surgery (HR: 0.44, 95%CI: 0.25-0.79) and peri-anal surgery (HR: 0.30, 95% CI: 0.16-0.56). Using propensity score matching, early IM significantly reduced surgical rates (HR: 0.54, 95%CI: 0.37-0.79). Number needed to treat to prevent a surgical event at 5-years from diagnosis and after initial surgery was 6.99 (95%CI: 5.34-11.95) and 8.59 (95%CI: 6.26-23.93) respectively.

Conclusion

Early IM use with thiopurines or methotrexate was significantly associated with the reduced need for abdominal and perianal surgery in Crohn's disease.

Keywords: azathioprine; thiopurine; mercaptopurine; immunomodulator; methotrexate; Crohn's disease; surgery; treatment; outcome

2.2 INTRODUCTION

Crohn's disease (CD) is a chronic, inflammatory gastrointestinal disorder with a high proportion of sufferers requiring abdominal surgery and recurrent surgery for relapsing disease. Intestinal resectional rates of up to 61% five years after the initial diagnosis have been reported.[1] A decline in surgical rates, hence possibly a change in the natural history of CD, has been associated with improved medical therapy.[2-6] Other studies, however, suggest that surgical rates have remained stable over time despite changes in medical treatment.[7-10] Most natural history studies are unable to demonstrate a positive impact of immunomodulator (IM), possibly due to their use in more severe disease, late introduction after development of strictures or fistulas, or insufficient patient-years of follow up. Two recent randomized controlled studies demonstrated a 'top-down' approach in the early introduction of thiopurines following CD diagnosis failed to reduce CD relapse compared to a convention 'step-up' approach in management.[11,12] However, the sample sizes were relatively small, follow-up period too brief and a high proportion of control subjects eventually required commencement of thiopurines, which may negate any benefit. In addition, most studies have focused only on the short term impact of thiopurines, which are recognized to fail, be complicated by drug-induced idiosyncratic and dose-related adverse effects or not tolerated in up to 40% of patients.[13] IM therapy in CD often involves thiopurines as first line therapy and methotrexate as second line treatment following failure of thiopurines.[14,15] Therefore to demonstrate the effectiveness of the early IM strategy on surgical outcomes, requires a study recruiting not only those on thiopurines but also methotrexate in those intolerant to-, had failed- or for whom thiopurines were contraindicated. Scrutinizing each case to ensure study definitions are met and confounding factors corrected for, is required. To these ends, a prevalence population study approach can provide the necessary case load, review of each and every case, and obtain sufficient follow up to ensure robustness of results.[16]

Australia has one of the highest reported incidence of CD in the world with a high surgical resection rate.[17,18] Reimbursement for anti tumor necrosis factor alpha (anti-TNF) was unavailable until 2008, and even after that time, complete failure of at least one IM (or intolerance to two IMs) was required prior to commencement of anti-TNF. As such, good characterization of the effects of IM

use on disease natural history is possible due to the high dependence on well-prescribed IM for their immunosuppressive and steroid-sparing effects. Additionally, Australian gastroenterologists were early adopters of thiopurine metabolite measurements and manipulation of 6-TGN levels through dose modification and addition of allopurinol for those with preferential shunting towards inactive thiopurine metabolites.[19] Methotrexate is typically used in those unsuccessfully treated with thiopurines unless contraindicated. Defined populations within Australia may therefore be an ideal setting to test the strategy of early IM use of thiopurines or methotrexate on the need for initial and recurrent surgery in CD.

Aims

The study hypothesis is that early IM use, comprising of either thiopurines or methotrexate for unsuccessful thiopurine usage, reduces initial and recurrent surgical rates in CD. The primary outcome measure assessed was the cumulative probability of major abdominal surgery for CD stratified by early IM use. The secondary outcome was the impact of early IM use on requirement for recurrent major abdominal surgery and perianal surgery.

2.3 Materials and methods

Patient recruitment

The "Sydney IBD Cohort" comprises a longitudinal cohort of patients first described in 1994.[20] Ambulatory patients were originally identified from histology records, pathology database, endoscopy database, medical health records and correspondence letters from Concord Hospital, Royal Prince Alfred Hospital and community gastroenterologists within the catchment region. The same methodology was replicated in 2010 to enrich the cohort and the registry was updated. Diagnoses were thoroughly reviewed retrospectively using the gastroenterologists' prospective-collected electronic and written case records, endoscopy, radiology, pathology and histology data.[21] To ensure complete data capture, only patients with a confirmed initial diagnosis of CD between January 1st 1970 and December 31st 2009 were recruited. This time period provided

sufficient patient-years of follow up of study outcomes and sufficient variation in the time to commence IM. All events occurring up until July 2012 were recorded.

CASE REVIEW AND COLLECTION OF DATA

Patient medical records were retrospectively reviewed for prospectively collected demographic data, disease characteristics, medication usage and surgical history. Demographic data included age, year of diagnosis, sex, and smoking status at diagnosis. Those lost to follow up were contacted and if unavailable, were censored as at their last observation. Disease characteristics within 6 months of the initial diagnosis were classified according to the Montreal Classification.[22] To assess the influence of decade of diagnosis on outcomes, patients were sub-grouped into Group A diagnosed between 1970-1979; Group B: 1980-89; Group C: 1990-99 and Group D: 2000-09. Medical therapy included 5 amino-salicylates (5-ASA), IM (azathioprine, mercaptopurine, methotrexate), anti-TNF therapy and long-term corticosteroid use, defined as 6 months or more of continuous- or a total of 8 months or more of discontinuous- use within a 12-month period. Data on IM included time to commencement from diagnosis, side effects and duration of exposure. Early IM use was defined as introduction of IM within 3 years of diagnosis and maintained for at least 6 months.[6,23] In assessing the occurrence of recurrent surgery, the identical definition was applied for post-operative IM use with the time period commencing from the date of prior surgery. Detail of surgical procedures and resections were collected including the time to surgery. Major abdominal surgery, the primary outcome measure, was defined as intestinal resection, stricturoplasty, explorative laparotomy, intra-abdominal abscess drainage and stoma formation. Planned two stage operations and reversal of stoma were included in the total number of procedures but were not considered as a recurrent major surgery for analysis. Perianal surgeries consisted of abscess drainage and insertion of setons for perianal fistulae. Simple examinations under anesthesia without abscess drainage were excluded.

TREATMENT WITH IMMUNOMODULATORS DURING THE STUDY PERIOD

Consistent with local practice, thiopurines were used as the first-choice IM, with azathioprine generally used ahead of mercaptopurine. Typical dosing of azathioprine was 2- 2.5mg/kg body weight, and for mercaptopurine it was 1-1.5mg/kg body weight. Dose reduction may have been required for intolerance. In recent years, thiopurine metabolite testing to titrate dosage and allopurinol co-therapy were used to optimize thioguanine nucleotide levels[19]. Methotrexate was used primarily as a second line therapy following failure of thiopurines, either orally or parenterally initiated at a dose of 25mg per week with maintenance dosing of 15mg per week. Third line IMs were not analyzed as they account for a negligible case load. After initiation, IM were prescribed indefinitely unless ceased due to failure, side effects, complications, patient non-adherence and/ or other patient circumstances.

STATISTICAL ANALYSIS, PROPENSITY SCORE MATCHING AND ETHICS

Description of continuous variables was by median and inter-quartile ranges (IQR). Categorical variables were presented as percentages and analyzed by the chi-square test. Survival analysis was calculated using the log rank score and data demonstrated using the Kaplan–Meier curve. Cox proportional hazards regression models (both univariate and multivariate) are expressed as hazard ratios (HR) with their 95% confidence intervals (CI).

Sensitivity analyses after strict propensity score matching was performed to control for possible confounders of treatment initiation for first major surgery. The propensity score method is a tool to adjust a treatment effect for measured confounders.[24] The propensity scores for each patient were based on the covariates identified to predict the early use of IM and additional covariates known to be associated with requirement of surgery but not identified to be associated with early IM use. Using the propensity scores, early IM users were matched to CD patients without early IM,

using a 1 to 2 greedy matching algorithm, with a proximity caliper of 0.5. Similar matching was performed after excluding patients who had surgery within 6 months of diagnosis. Goodness of fit was evaluated by Hosmer-Lemeshow test and the *P* Values were non-significant. Effect on early IM use on the time to surgery was assessed after propensity matching and expressed as HR with 95% CI. A *P* value of <0.05 was considered statistically significant. Number needed to treat (NNT) to prevent a surgical event at five years from diagnosis and after initial surgery was based on the reported HR and survival at five years (SC5) in the control group (NNR = $1/(SC5^{HR} - SC5)$.[25] Sample size target aimed to exceed similar published population-based cohorts that have recruited 310[7] to 506[6] CD cases with median follow up for all time periods must be of at least 5 years. Statistical analysis was performed using IBM SPSS software version 20.0. The Sydney Local Health District Human Research Ethics Committee approved this study (HREC/10/CRGH/126).

2.4 Results

Patient characteristics

A total of 1,035 consecutive CD patients were recruited with median patient follow-up of 11.0 years (IQR 5.0-19.0) and a collective follow-up of 13,061 patient-years. The patient characteristics at diagnosis are displayed in table 2.1. Baseline characteristics at diagnosis remained similar across the decades of diagnosis apart from a non-significant trend towards increases in the prevalence of perianal and upper gastrointestinal disease locations (both *P*=0.07).

Medical interventions

The overall prevalence of 5-ASA, long-term corticosteroids and anti-TNF therapy was 87.4%, 61.6% and 12.2% respectively (Table 2). Use of 5-ASA and long-term corticosteroids reduced significantly over time (*P*<0.0001). A total of 437 (44.4%) patients were started on IM and of these, 384 patients (87.9%) continued treatment for six months or more, with a median duration of exposure of 2

years (range 0-33) (Table 2.2). Immunomodulators used were thiopurines in 84.0% of cases and methotrexate in 14.9%, initiated following failure of thiopurines. Only 1.1% of CD subjects were initiated on methotrexate alone due to unfavorable thiopurine methyltransferase enzyme pharmacogenomics predictive of myelotoxicity and for concurrent treatment of inflammatory arthritic extra-intestinal manifestation of CD. The median duration of disease at the time of IM commencement decreased from 26.5 years in Group A to 1.0 year in Group D (P<0.0001). The probability of being maintained on IM at 1 and 5 years increased from 1.3% and 1.3% in Group A, 0.4% and 2.5% in Group B, 8.3% and 26.3% in group C and 35.8 and 55.3% in Group D (P<0.0001; Figure 2.1).

On univariate analysis, the age of diagnosis phenotype A1 (age of onset ≤ 16 years) and A2 (17 to 40 years) predicted for early use of IM (HR: 2.98, 95% CI: 2.06-4.31, P<0.0001 and HR: 1.77, 95% CI: 1.36-2.3, P<0.0001 respectively). Other predictors of early IM use included: colonic disease location (HR: 0.77, 95% CI: 0.61-0.98), upper gastrointestinal disease location (HR: 2.76, 95%CI:1.55-4.92, P=0.001), perianal disease (HR: 1.66, 95% CI: 1.33-2.09, P<0.0001), 5-ASA use (HR: 0.73, 95% CI: 0.55-0.96, P=0.026), long term corticosteroid use (HR: 1.5, 95% CI: 1.21-1.87, P<0.0001), anti-TNF exposure (HR: 3.56, 95% CI: 2.84-4.55, P<0.0001) and more recent time-period of diagnosis (HR: 3.44, 95% CI: 2.93-4.04, P<0.0001). On multivariate Cox proportional hazard regression analysis, the significant independent predictors of early IM use were young age of diagnosis below 16 years (HR: 2.44, 95% CI: 1.66-3.60) and 16 to 40 years (HR: 1.59, 95% CI: 1.21-2.09), long-term corticosteroid use (HR: 1.83, 95% CI: 1.45-2.31), anti-TNF exposure (HR: 1.82, 95% CI: 1.41-2.36), and the most recent decades of diagnosis (HR 0.02 to 0.33, all P<0.0001; Table 2.3).

MAJOR ABDOMINAL SURGERY

A total of 388 (37.5%) had at least one major abdominal surgery, with 18.8% of these occurring within 6-months of diagnosis. Of those who had at least one recurrent operation, 117 (30.2%) underwent 2 or more major abdominal surgeries. A total of 9.2% of patients underwent perianal

surgery, with 28.4% of these requiring repeat procedures. The types of surgical procedures performed remained similar across all study decades (Table 2.4). The risks of major abdominal surgery at 1, 5 and 10 years after diagnosis were 17.5%, 28.4% and 39.5%. The risks of recurrent surgery at 1, 5 and 10 years after the first surgery were 5.9%, 19.0 % and 33.3% respectively.

FACTORS ASSOCIATED WITH FIRST MAJOR ABDOMINAL SURGERY

All baseline characteristics at diagnosis and medication use were considered for the univariate analyses. Early IM use (P<0.0001), long-term corticosteroid use (P=0.001), 5-ASA use (P<0.0001), age of diagnosis (P<0.0001), location phenotype (P<0.0001), behavioral phenotype (P<0.0001) and decade of diagnosis (P=0.002) were each significantly associated with time to major abdominal surgery (Supplement 1). Anti-TNF use, gender, smoking, perianal involvement, upper gastrointestinal disease location and extra-intestinal manifestations at diagnosis were not associated with time to first major abdominal surgery.

On multivariate analysis, early IM use was associated with decreased need for first major abdominal surgery (HR: 0.45, 95% CI: 0.32-0.63, P<0.0001) (Table 2.5). Colonic disease location (HR: 0.36, 95% CI: 0.27-0.50, P<0.0001) and 5-ASA use (HR: 0.56 95% CI: 0.41-0.76, P<0.0001) were also associated with decreased need for surgery. Stricturing disease behaviour (HR: 2.48, 95% CI: 1.93-3.20, P<0.0001), penetrating disease behaviour (HR: 2.97, 95% CI: 2.14-4.11, P<0.001) and long-term corticosteroid use (HR: 1.41, 95% CI: 1.12-1.78, P=0.004) were associated with increased need for first major abdominal surgery. Neither the decade of diagnosis nor the age at diagnosis were significant independent predictors of surgery. The NNT with IM to prevent a surgical event at five years was 6.99 (95%CI: 5.34-11.95).

PROPENSITY SCORE MATCHING AND SENSITIVITY ANALYSIS

A propensity score model was developed to quantify early IM use, using the factors predictive of early IM use and additional factors identified to affect surgical outcome. A total of 173 (96%) early IM users were matched against 266 controls that did not receive early IM. The mean propensity score of treated and controls were 0.42 and 0.15 before matching and 0.41 and 0.35 after matching. After matching, the relative multivariate imbalance improved from 0.73 to 0.58. Further matching was performed after excluding patients who had major abdominal surgery within 6 months of diagnosis, as IM therapy during this time may not have had sufficient time to reach peak efficacy to prevent surgery. A total of 165 (89%) of early IM users were matched against 251 controls. The relative multivariate imbalance improved from 0.66 to 0.43 after matching. In the propensity-matched analysis, early IM use was significantly associated with the requirement for first major abdominal surgery in the overall cohort (HR: 0.54; 95% CI: 0.37-0.79, *P*=0.002) (Figure 2.2A) and also after excluding patients who had surgery within 6 months of their diagnosis (HR: 0.64; 95% CI: 0.42-0.96, *P*=0.034).

FACTORS ASSOCIATED WITH RECURRENT MAJOR ABDOMINAL SURGERY

All baseline characteristics at diagnosis and medication use were considered for the analysis. On univariate analysis, early IM use after first major abdominal surgery (*P*=0.014, Figure 2.2B), anti-TNF use (*P*=0.024) and long-term corticosteroid use (*P*=0.024) were all associated with time to recurrent surgery. Decade of diagnosis was not associated with time to recurrent surgery (*P*=0.375). On multivariate analysis, early IM use after the first surgery predicted reduced need for recurrent surgery (HR: 0.44, 95% CI: 0.25-0.79, *P*=0.006). Anti-TNF use, however, was associated with an increased risk of recurrent surgery (HR: 1.7, 95% CI: 1.01-2.87, *P*=0.047). The NNT with IM post-surgery to prevent reoperation at 5 years was 8.59 (95%CI: 6.26-23.93).

FACTORS ASSOCIATED WITH PERIANAL SURGERY

On univariate analysis early IM was associated with the reduced need for perianal surgery (P=0.008, Figure 2.2C). On multivariate analysis early IM use remained an independent predictor of reduced need for perianal surgery (HR: 0.30, 95% CI: 0.16-0.56, P<0.0001). Anti-TNF use (HR: 1.73, 95%CI: 1.06-2.83, P=0.029), long-term steroid use (HR: 1.71, 95%CI: 1.03-2.83, P=0.038) and most recent decade of diagnosis (HR: 3.18, 95% CI: 1.59-6.33, P=0.001) were associated with increased need for perianal surgery.

2.5 DISCUSSION

In this Australian specialist-based cohort study with sufficient sample size and duration of follow up, significant reduction in the risk of initial and recurrent major abdominal surgery for CD were observed with the use of early IM therapy. Importantly, rather than simply being associated with treatment paradigm changes in recent decades, the reduction in surgery was independently and significantly associated with the early introduction of IM therapy within 3 years of diagnosis and maintained for at least 6 months. Immunomodulator therapy was also defined by prescription of at least 6 months prior to the first major surgery to avoid biases of late and futile introduction of the drug.[10] Even adjusting for possible biases through rigorous analysis with propensity score matching and exclusion of subjects who required surgery within 6 months of diagnosis, significant reductions in both initial and recurrent surgery were observed. These findings support a possible change in the natural history of CD resulting from early- and sustained IM early after diagnosis and after surgical intervention and were independent to the decade of diagnosis. Early IM therapy was also identified as the most significant independent predictor of the need for perianal surgery.

In Australia, the limitations on the use of anti-TNF agents have led to the increased reliance on- and earlier introduction of IM. Although IM comprised almost universally of thiopurines as first-line agent, poor response, intolerance, hypersensitivity, idiosyncratic and dose-related adverse reactions required the introduction of methotrexate as part of the IM strategy. This may increase the capture of subjects who benefit from early IM therapy and the strategy might have been responsible for the reduction in major abdominal surgery in CD.

In the pediatric CD population, early introduction of azathioprine decreased the need for surgery.[24] However, in an adult population study from France no reduction in the surgical resection rate was found despite an increase in the use of azathioprine over time[10,26]. The latter study has been criticized for commencing IM too late in the disease course and hence being unable to modify disease natural history. A population-based study from Cardiff identified a significant reduction in surgical rates among patients diagnosed with CD between 1986-2003 that was independently associated with early introduction of azathioprine.[2] However, the year of diagnosis was an independent predictor of surgery indicating that changes in surgical treatment paradigms over time may have been responsible for the reduction in surgical rates. The protective effect of IM was also demonstrated by Lakatos *et al* in a recently published study from western Hungary, in which early commencement of azathioprine was found to reduce the need for first surgery independent to the decade of diagnosis[6]. Strict definitions for early IM use and propensity score matching to eliminate bias in their study design were applied, as was the case in the present study, and correcting for biases may differentiate our results from the previously-published negative studies.

The benefit of thiopurines in preventing post-operative recurrence has been demonstrated in clinical trial settings.[27,28] However, population based studies have yet to confirm this benefit.[7] A recent retrospective analysis demonstrated a significant reduction in post-operative recurrence associated with azathioprine exposure for at least 36 months, initiated between 3 to 60 months after the initial surgery[29]. The study could be criticized for not addressing the immortal time bias

favoring azathioprine. To correct for this bias in studying whether IM can reduce the need for recurrent surgery, we only included IM use within 3 years of the index major abdominal surgery that was maintained for at least 6 months. Using these strict definitions, we have demonstrated the benefit of early IM use in preventing surgical recurrence.

The increased risk of recurrent surgery and perianal surgery associated with use of anti-TNF therapy must be interpreted with caution, given its use at the time of patient recruitment was prior to their regulatory approval for reimbursement. Anti-TNF treatments were given on an episodic basis and reserved for complicated and severe disease late in the disease course. Since that time, biological therapies have been given in accordance to best practice as scheduled maintenance and earlier in the course of disease.[30] Even with scheduled maintenance biological agents, they may be associated with high-cost, risk of severe adverse reactions including life-threatening infections, primary non-response in a-third of patients and progressive secondary loss of response. [30-32] As such, effective, cheaper, and easy-to-administer IM medications that can be prescribed with a high-level of confidence by physicians, are required[33].

There are a few limitations of this study. The study population was an ambulatory non-hospital-based specialist referred cohort, based within the Sydney Local Health District rather from national databases. However, recruitment of ambulatory patients managed continuously by gastroenterologists with excellent longitudinal follow up and documentation allowed for excellent characterization of every case and ensured the definition of IM was met. Similar strategies have been employed in other Australian and New Zealand population-based cohorts.[17,34] Reassuringly, the 1, 5 and 10-year risk of first surgery in the current cohort are similar to the pooled 1, 5 and 10-year risk of surgery published from a meta-analysis of population-based studies[35]. The recruitment strategy also provided sufficient patient-years of follow up required to not only demonstrate initial surgical rates within 5 years of diagnosis, but also recurrent surgical rates that few studies have published to date. Scrutiny of individual cases is often not possible using larger population cohorts and misclassification may confound results. Despite having greater scrutiny, the lack of smoking

data in over 400 patients emphasizes the difficulties in conducting a retrospective study spanning 40 years. This may account for smoking not been identified as a risk factors for surgery in the current cohort. Secondly, patient management strategies and diagnostic tests have changed over time and may have accounted for changes in surgical rates. This, however, was corrected-for by including "decade of diagnosis" as a variable in the multivariate analysis, which failed to be an independent predictive variable for surgery. Early IM use was the only controllable factor that significantly decreased initial and recurrent major abdominal surgery in CD. Thirdly, this was not a randomized placebo-controlled study. However, such studies may be limited with their patient-years of follow up in identifying surgical events and the need for recurrent surgeries. In their control groups, high proportions of controls eventually required commencement of thiopurines.[11,12] Such studies may require per protocol analysis, very large sample sizes studied over many years to identify the true benefits of thiopurines. These studies also did not take into account the possible benefit of second-line methotrexate following the high dropout rates that occur with thiopurine treatment. This study ensured the robustness of the diagnosis, conformity of evidence-based management and case definitions that may be lacking in studies derived from insurance data, hospital coding or de-identified data that cannot be verified. Lastly this study was not designed to be analyzed according to intention-to-treat. The duration of IM use criteria had to be met on a per protocol basis in order to test the absolute benefit of early IM therapy over time. Reasons for ceasing IM therapy, although not specifically reported here, were similar to those previously published.[13]

The strengths of this study included the large size of the cohort, the long duration of follow-up, and the completeness of disease characterization from the initial point of contact. Rigorous monitoring and validation of data capture was possible. This is the first study that included methotrexate use for those who had failed thiopurines to test the real-life option of the IM strategy. The IM strategy has been well verified in this and other studies to have steroid-sparing effects, but this study adds to the few that demonstrate significant reduction in both initial and recurrent surgery associated with their earlier initiation and sustained use. This study is also one

of only a few to use propensity score matching to correct for biases, which may reduce type II errors and also to calculate the NNT to prevent a surgical event. Given their low cost in comparison to biological agents and expensive and disabling surgical events, IM therapy needs to be advocated to remain within the armamentarium for the treatment of IBD.[33] Data to demonstrate absolute improved outcomes, however, are also needed to support their use given their known risk of adverse events. These data support the earlier introduction of thiopurines and methotrexate for those that fail thiopurines in CD.

In conclusion, early and sustained use of IM after diagnosis and after surgery was significantly associated with a reduction in the risk of abdominal and perianal surgery in CD. The results on abdominal surgery are independent to decade of diagnosis suggesting a true drug-induced beneficial effect in improving long-term outcomes and support their ongoing use in the treatment of CD.

Table 2.1: Clinical characteristics at diagnosis grouped according to the decade of diagnosis

	Total 1970-2009	Group A 1970-1979	Group B 1980-1989	Group C 1990-1999	Group D 2000-2009	P
Number of patients	1035	90	286	276	383	
Median follow-up in years (IQR)	11(5-19)	29 (18-35.5)	20 (9-25)	14 (11-18)	5 (2-7)	<0.0001
Patient years of follow-up	13061	2400	4955	3712	1994	
Gender N (%)						0.21
Male	450 (43.5)	31(34.4)	119 (41.6)	125 (45.3)	175 (45.7)	
Female	585 (56.5)	59 (65.6)	167 (58.4)	151 (54.7)	208 (54.3)	
Median age at diagnosis (Range)	29 (5-92)	28 (8-72)	28 (6-92)	30 (5-84)	30 (6-87)	0.28
Age N (%)						0.16
Less than 16 years (A1)	76 (7.3)	5 (5.6)	21 (7.3)	16 (5.8)	34 (8.9)	
Between 17 and 40 years (A2)	653 (63.1)	68 (75.6)	179 (62.6)	171 (62.0)	235 (61.4)	
Age more than 40 years (A3)	306 (29.6)	17 (18.9)	86 (30.1)	89 (32.2)	114 (29.8)	
Disease location N (%)						0.52
Ileal (L1)	247 (24.0)	23 (25.6)	63 (22.1)	63 (23.1)	98 (25.8)	
Colonic (L2)	388 (37.7)	23 (25.6)	109 (38.2)	112 (41.0)	144 (37.9)	
Ileo-colonic (L3)	393 (38.2)	44 (48.9)	113 (39.6)	98 (35.9)	138 (36.3)	
Not documented	7					
Gastro-duodenal (L4)	17 (1.7)	0	1 (0.4)	6 (2.2)	10 (2.6)	0.07
Not documented	11					
Disease behaviour N (%)						0.52
Non-stricturing/ non-penetrating (B1)	697 (68.5)	52 (65.8)	186 (66.4)	196 (71.0)	263 (68.7)	
Stricturing (B2)	224 (22.0)	22 (27.8)	69 (24.6)	53 (19.2)	80 (20.9)	
Penetrating (B3)	97 (9.5)	5 (6.3)	25 (8.9)	27 (9.8)	40 (10.4)	
Not documented	17					
Peri-anal disease N (%)						0.07
Yes	191 (18.5)	9 (10.3)	46 (16.1)	55 (19.9)	81 (21.1)	
No	840 (81.5)	78 (89.7)	239 (83.9)	221 (80.1)	302 (78.9)	
Not documented	4					
Extra-intestinal manifestations N (%)						0.10
Yes	191 (18.6)	16 (18.6)	60 (21.2)	38 (13.8)	77 (20.2)	
No	836 (81.4)	70 (81.4)	223 (78.8)	238 (86.2)	305 (79.8)	
Not documented	8					
Smoking status N (%)						0.51
Current smokers	118 (20.1)	2 (11.1)	16 (26.2)	38 (20.5)	62 (19.2)	
Ex-smokers	140 (23.9)	7 (38.9)	15 (24.6)	46 (24.9)	72 (22.3)	
Never-smokers	329 (56.0)	9 (50.0)	30 (49.2)	101 (54.6)	189 (58.5)	
Not documented	448					

Table 2.2: Drug therapy during follow-up grouped according to decade of diagnosis (N (% within time period)

	Total 1970-2009	Group A 1970-1979	Group B 1980-1989	Group C 1990-1999	Group D 2000-2009	P Value
Long-term corticosteroid	590 (59.2)	67 (77.0)	200 (72.5)	149 (58.0)	174 (46.2)	<0.0001
5-aminosalicylate	884 (86.3)	81(95.3)	263 (93.6)	247 (89.8)	293 (76.5)	<0.0001
Anti-TNF	110 (10.6)	2 (2.2)	9 (3.1)	34 (12.4)	65 (17.0)	<0.0001
Immunomodulators	384 (39.0)	9 (12.0)	45 (18.0)	122 (44.2)	208 (54.3)	<0.0001
Immunomodulators within first year of diagnosis	163 (16.6)	1(1.3)	2 (0.8)	23 (8.3)	137 (35.8)	<0.0001
Early use of immunomodulators	189 (19.2)	0	3(1.2)	45 (16.3)	141 (36.8)	<0.0001
Exposed immunomodulator						0.957
Thiopurine	367 (84.0)	8 (80.0)	43 (82.7)	118 (83.1)	198 (85.0)	
Methotrexate	5 (1.1)	0	0	2 (1.4)	3 (1.3)	
Both	65 (14.9)	2 (20.0)	9 (17.3)	22 (15.5)	32 (13.7)	
Median time to starting immunomodulators (years)	2	26.5	14	4.5	1	<0.0001

Table 2.3: Factors affecting time to initiation of immunomodulator therapy in Crohn's disease on Cox proportional hazard regression

	P value	Hazard Ratio	95% CI
Age of diagnosis	<0.0001		
<16	<0.0001	2.44	1.66-3.60
16-40	<0.001	1.59	1.21-2.09
>40	Reference		
Location at diagnosis	0.084		
Ileal	0.72	1.05	0.81-1.37
Colonic	0.062	0.79	0.62-1.01
Ileo-colonic	Ref		
Perianal involvement	0.017	1.33	1.05-1.68
Long-term corticosteroid use	<0.0001	1.83	1.45-2.31
Anti TNF exposure	<0.0001	1.82	1.41-2.36
Decade of diagnosis	<0.0001		
1970-1979	<0.0001	0.02	0.01-0.06
1980-1989	<0.0001	0.07	0.05-0.11
1990-1999	<0.0001	0.33	0.25-0.43
2000-2009	Reference		
Removed from the model: 5-ASA use (*P*=0.75) and upper gastrointestinal disease location (*P*=0.39)			

Table 2.4: Types of first major abdominal surgery performed for Crohn's disease at any time during follow-up

Procedure type	N (%)
Ileo-caecal resection/ Right hemi-colectomy with ileal resection	219 (56.4)
Segmental resection of small bowel	67 (17.3)
Sub-total colectomy and colostomy	7 (1.8)
Total/ sub-total colectomy and ileostomy	47 (12.1)
Loop ileostomy / colostomy	11 (2.8)
Sub-total colectomy and ileo-rectal anastomosis	30 (7.7)
Stricturoplasty	3 (0.8)
Total colectomy and pouch formation	2 (0.5)
Abdominal exploration / abscess drainage	2 (0.5)

Table 2.5: Factors affecting time to time to first major abdominal surgery in Crohn's disease on Multivariate Cox proportional hazard regression

	P value	Hazard Ratio	95% CI
Early IM use	<0.0001	0.45	0.32-0.63
Long term steroid use	0.004	1.41	1.12-1.78
5 ASA use	<0.0001	0.56	0.41-0.76
Location at diagnosis	<0.0001		
Ileal	0.244	1.16	0.91-1.48
Colonic	<0.0001	0.36	0.27-0.50
Ileo-colonic	Ref		
Behaviour at diagnosis	<0.0001		
Inflammatory	Ref		
Stricturing	<0.0001	2.48	1.93-3.20
Penetrating	<0.0001	2.97	2.14-4.11
Removed from the model: age at diagnosis (*P*=0.239), decade of diagnosis (*P*=0.309)			

Supplement 2.1. Factors affecting time to time to first major abdominal surgery in Crohn's disease univariate analysis

	P value	Hazard Ratio	95% CI
Gender	0.336	1.10	0.90-1.35
Smoking status	0.434		
Never	Ref		
Current	0.213	1.24	0.88-1.75
Ever but not current	0.450	1.14	0.82-1.58
Age at diagnosis	<0.0001		
<16	0.001	1.96	1.33-2.88
17-40	<0.0001	1.67	1.30-2.15
>40	Ref		
Location at diagnosis	<0.0001		
Ileal	0.210	1.15	0.92-1.44
Colonic	<0.0001	0.26	0.19-0.34
Ileo-colonic	Ref		
Upper GI involvement	0.064	0.27	0.07-1.08
Behaviour at diagnosis	<0.0001		
Inflammatory	Ref		
Stricturing	<0.0001	3.49	2.79-4.37
Penetrating	<0.0001	3.76	2.79-5.08
Perianal involvement	0.81	0.97	0.75-1.25
EIM at diagnosis	0.34	0.88	0.67-1.15
Early IM use	<0.0001	0.50	0.36-0.71
Long term steroid use	0.001	1.46	1.17-1.83
5ASA use	<0.0001	0.55	0.42-0.72
Anti TNF use	0.213	1.21	0.90-1.64
Decades of diagnosis	0.002		
1970-1979	<0.0001	1.85	1.33-2.59
1980-1989	0.026	1.36	1.04-1.79
1990-1999	0.344	1.15	0.86-1.53
2000-2009	ref		

Figure 2.1: Immunomodulator use according to the decade of diagnosis in patients with Crohn's disease (*P*<0.0001)

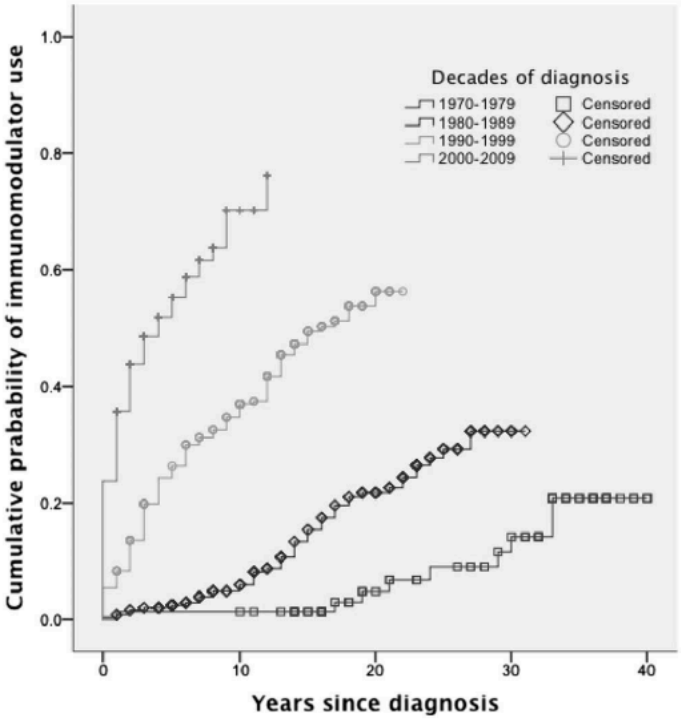
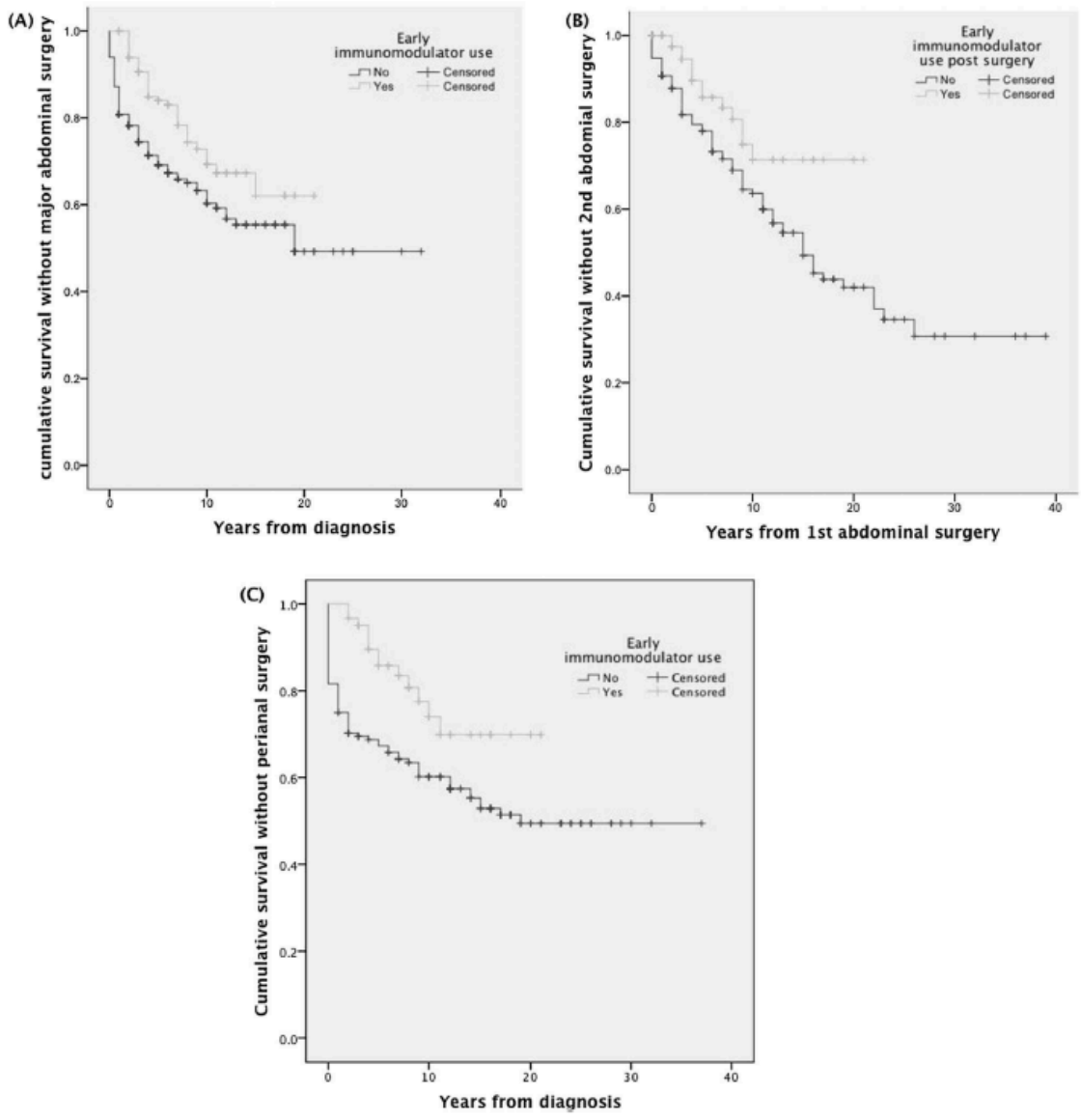


Figure 2.2: (A) Association between early immunomodulator use and major abdominal surgery after propensity matching (*P*=0.001) (B) Association between early immunomodulator use and second major abdominal surgery (*P*=0.014) (C) Association between early immunomodulator use and perianal surgery (*P*=0.008)



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CHAPTER 3 : (STUDY2) IMPACT OF EARLY THIOPURINE MAINTENANCE, ON THE RATE OF COLECTOMY AND PROXIMAL PROGRESSION OF DISEASE EXTENT IN ULCERATIVE COLITIS

The content of this chapter is presented as a manuscript submitted for publication to Journal of Crohn's and Colitis "Early Sustained Maintenance of Thiopurine Reduces Colectomy Rate and Progression of Disease Extent in Patients with Ulcerative Colitis

Early Maintenance of Thiopurine Reduces Colectomy Rate and Proximal Progression of Disease Extent in Patients with Ulcerative Colitis

(Short title- Early Thiopurine Therapy in Ulcerative Colitis)

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Non-Standard abbreviations:

AZA – Azathioprine

MP – Mercaptopurine

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Contribution:

VK contributed to study design, data acquisition, analysis, and wrote and revised the manuscript. FM contributed to analysis and writing up of the manuscript. CS, PK, BJ, CM, GB, GC, JC, SP and JA contributed to data acquisition and manuscript revision. RL contributed to study design, manuscript revision and intellectual content.

What is already known about this subject?

- Recent population-based studies have shown decreased colectomy rates in patients with ulcerative colitis
- The decline in colectomy rates occurred prior to biological agents becoming widely available
- Thiopurines are effective as steroid sparing drugs in ulcerative colitis. Whether early initiation of thiopurines after diagnosis decreases proximal disease progression and colectomy rates are not well known

What are the new findings?

- Early thiopurines maintenance was associated with a 90% reduction in the probability of colectomy using a propensity score model.
- Number of subjects needed to be treated to prevent one colectomy at 5 and 10 years was 18 and 12
- Proximal progression of disease extent was associated with 2.2-fold increase risk of colectomy
- Early thiopurine maintenance was associated with a 71% reduced risk of proximal progression of disease extent.

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

- Thiopurines should be considered early on in the treatment of ulcerative colitis, as a steroid sparing agent, as well to prevent proximal disease progression and decrease colectomy rates.
- Patients with proctitis and left sided colitis should be closely followed up as disease progression is associated with a significant increase in the risk of colectomy.

3.1 Abstract

Background

Thiopurines effectively maintain remission in ulcerative colitis (UC) patients. Whether early initiation of thiopurines after UC diagnosis decreases proximal disease progression and colectomy rates is not known.

Methods

We conducted a cohort study of UC subjects recruited from 1970 to 2009. Early thiopurines maintenance was defined as commencement of azathioprine or mercaptopurine within 5-years of diagnosis and maintenance for at least 6-months. Propensity score matching was conducted to correct for confounders influencing early thiopurine introduction. Outcomes of interest were colectomy rate and endoscopic proximal disease extension.

Results

982 consecutive UC subjects (12,879 patient-years) were recruited with 116 requiring colectomy. Thiopurines initiation and maintenance increased over time with median time to thiopurine commencement decreasing from 23 years in the first decade to 2 years in the last decade (P<0.0001). Multivariate analysis showed that early thiopurine maintenance significantly decreased the need for colectomy (hazard ratio [HR]: 0.13; 95% confidence interval [CI]: 0.03-0.55; P=0.006). The number of subjects needed to be treated to reduce one colectomy at 5 and 10 years was 18 (95% CI: 16-36) and 12 (95%CI: 11-25). After propensity score matching, early thiopurine maintenance was significantly associated with decreased colectomy (HR: 0.10, 95%CI: 0.03- 0.43, P=0.002) and proximal progression of disease extent (HR: 0.26, 95%CI: 0.10-0.78, P=0.015).

CONCLUSIONS

Early thiopurine maintenance for > 6 months is significantly associated with reduced colectomy and with proximal progression of disease extent in UC.

3.2 Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with a prevalence of 17.4 per 100,000 [1, 2] with 70-90% of patients following a continuous or relapsing-remitting course [3, 4]. Conventional treatment of mild-to-moderate UC includes mesalazine [5] but more severe UC may require systemic corticosteroids, azathioprine, mercaptopurine, anti-tumour necrosis factor agents (infliximab, adalimumab, golimumab) or the anti-integrin vedolizumab [5].

Historically, colectomy rates were reported at 46 % of all patients with extensive chronic UC, within the first 10 years of diagnosis [4]. However, more recent population-based colectomy rates show lower colectomy rates of 15% at 10 years and 31% at 30 years [6]. The decline in colectomy rates occurred prior to biological agents becoming widely available. Therefore, the increasing and earlier use of thiopurines over time may be responsible for the reduced need for colectomy. In Crohn's disease (CD), early and sustained use of immunomodulators (IM) has been shown to significantly reduce the rates of major abdominal, perianal or recurrent surgery [7, 8]. The odds ratio (OR) for CD surgery was 1.006 (95% confidence interval [CI] 1.004-1.008) for each month of delay in starting thiopurines [7]. In UC, whether early sustained use of thiopurines reduces the need for colectomy or proximal progression of disease extent on colonoscopy is not established. Earlier commencement of thiopurines to control colitis may reduce progressive intestinal damage. The role for thiopurines in the management of IBD has been questioned with the advent of biological agents [9]. However, thiopurines are cheap and widely available in comparison to biological agents. Primary non-response and secondary loss of response result in lower persistence of biological agents and therefore more durable treatments are required. In developing parts of the world where IBD prevalence is increasing, tuberculosis rates are high and limitations exist in the reimbursement of high-cost medications, thiopurines may be an important treatment for UC [10].

The aim of maintenance therapy is to decrease flares, decrease the need for corticosteroids, and increase mucosal healing. Intestinal damage is a recognised result of IBD and may be irreversible [11]. Therefore, we aimed to determine whether commencement of thiopurine maintenance therapy within 5 years of diagnosis of UC prior to the development of irreversible submucosal fibrosis and intestinal damage [11], can reduce progression of colitis and colectomy.

We hypothesised that early maintenance of thiopurines may reduce colectomy rates in UC patients. The primary outcome measure was cumulative probability of colectomy in UC stratified by early thiopurines maintenance. The secondary outcome was the impact of early thiopurines maintenance on proximal progression of disease extent.

3.3 Materials and Methods

Patient recruitment

The 'Sydney IBD Cohort' is a longitudinally collected cohort of ambulatory subjects recruited from central Sydney as part of the Sydney Local Health District. Recruitment was from medical records (paper and electronic), endoscopy database, pathology database and correspondence letters from Concord Repatriation General Hospital, Royal Prince Alfred Hospital and community gastroenterologists within the Sydney Metropolitan region, using the prospectively collected electronic and written case records, endoscopy, radiology, pathology and histology data [12] of the gastroenterologists. The cohort was first described in 1994 [13] and data was updated using the same methodology in 2010 and 2012 to expand the cohort [6, 8, 14, 15]. Subjects were defined using Copenhagen criteria [16]. This time period was selected to allow for sufficient patients-years of follow up and complete dataset for the assessment. Prior to 2009, biological therapies were not reimbursed in Australia, so subjects were rarely prescribed. However, a few UC subjects received on-demand non-sustained therapy for refractory disease.

DATA COLLECTION

Prospectively collected demographic data, disease characteristics, medication usage and surgical history were obtained from patient medical records. Age, year of diagnosis, sex and smoking status were included in demographic data. Patients lost to follow up were contacted and were censored as at their last observation if unavailable. Patients with IBD-unclassified and a change in their diagnosis to non-IBD pathology were excluded. Montreal classification [17] was used to classify disease characteristics at baseline and/or within 6 months of first diagnosis. Changes in disease extent during follow up were recorded using endoscopy and imaging data. Disease extension from proctitis to left sided colitis or pancolitis and left sided colitis to pancolitis, was considered as proximal disease extension. Influence of decade of diagnosis on outcomes were assessed by patient sub-groups with Group A diagnosed between 1970-1979, Group B between 1980-89, group C between 1990-99 and Group D between 2000-09.

Mesalazine, IMs (azathioprine, mercaptopurine, methotrexate), anti-TNF therapy (adalimumab and infliximab) and long-term corticosteroid use, defined as 6-months or more of continuous, or total of 8 months or more of discontinuous use within a 6-month period, was collected. IMs data included time to initiation from diagnosis, side effects and period of exposure. To assess the impact on surgery and disease progression, early thiopurines maintenance was considered. Early thiopurines maintenance was defined as introduction of thiopurines within 5 years of diagnosis and maintained for at least 6-months prior to surgery. Patients who started thiopurine after 5 years, were included in the non-exposed arm. Subjects with methotrexate maintenance were excluded from the analysis, due to recent studies demonstrating methotrexate not to be superior to placebo in maintenance therapy in UC [18]. The primary outcome measure was colectomy due to UC, which was defined as bowel resection due to UC activity and not from dysplasia. Data on time to surgery and specifics of surgical procedures and resections were collected. Patients who had emergency colectomy at presentation and colectomy for the diagnosis of cancer were excluded from factors associated surgery analysis as they did not test the strategy of thiopurines controlling disease activity.

TREATMENT WITH THIOPURINES DURING THE STUDY PERIOD

In Australia, the first choice of thiopurines historically was AZA and this was used more commonly than MP. Thiopurines were started in patients who were steroid dependent or had active disease while on maintenance therapy with mesalamine or in high risk patients as determined by the treating gastroenterologist, based on the clinical presentation. Dosage of thiopurines was weight-based (AZA 2-2.5mg/kg and MP 1-1.5mg/kg) and guided by thiopurine metabolite testing (with target thioguanine nucleotide level of 235-450 units) or a lower dose if thiopurine was not tolerated. To achieve the target thioguanine nucleotide level some subjects received split dosing or thiopurine dose reduction combined with allopurinol co-therapy. Thiopurine therapy was continued indefinitely after initiation except in a few, unless stopped due to failure, side effects, complications, patient non-adherence, and/or other circumstances. Thiopurine maintenance was confirmed using history and prescription data.

STATISTICAL ANALYSIS, PROPENSITY SCORE MATCHING AND ETHICS

Continuous variables were described by median and interquartile ranges (IQR), while categorical variables were shown as percentages and analysed by chi-square test. Survival analysis was performed using log-rank score and displayed by the Kaplan-Meier method. Univariate and multivariate cox proportional hazards regression models were performed, expressed as hazard ratios (HR) with respective 95% confidence intervals (CI). Covariates identified a priori with $P < 0.1$ on univariate analysis were entered into a multivariate backward stepwise model.

Using propensity scoring allows for adjustment of treatment effect for measured confounders [19]. Strict propensity score matching was thus performed to control for possible confounders of early thiopurines initiation through selection bias of treatment trends based on era. Covariates recognised to predict early use of IM were used as the basis for propensity scores for each patient. Effect of early thiopurines maintenance on time to surgery and proximal progression of disease

were assessed after propensity matching and expressed as hazard ratio (HR) with 95% confidence interval (CI). A P-value of <0.05 was considered statistically significant. Number needed to treat (NNT) to prevent a surgical event at 5 years from diagnosis and after initial surgery was based on the reported HR and survival at 5 years (NNR= $1/[SC5^{HR} - SC5]$) [20]. IBM SPSS software version 25.0 was used to perform statistical analysis. The Sydney Local Health District Human Research Ethics Committee approved this study (HREC/10/CRGH/126).

3.4 Results

A total of 982 patients with UC were recruited with median follow up of 11.0 years (IQR: 5-20) and a collective follow up of 12,879 patient-years. Table 3.1 displays the patient characteristics at diagnosis showing similar baseline characteristics across the 4 decades of diagnosis. The majority of patients were never-smokers (71.3%) and 58.6% were diagnosed between the ages of 17-40 years. The diagnosis of pancolitis was more prevalent in the decade 1970-1979 compared to other decades (P<0.0001).

Medications

The overall prevalence of mesalazine, thiopurines, long term corticosteroids, and anti-TNF therapy use was 96.6%, 18%, 37.9% and 2.5% respectively (Table 3.2). Long term steroid use significantly decreased over time (P<0.021) while thiopurine-use increased significantly (P<0.0001) (Figure 3.1). The total number of subjects started on thiopurines were 177 and of these, 127 subjects (71.7%) were maintained on thiopurines for 6-months or more. The time to commencing thiopurines became earlier over the 4 decades (Figure 3.1). The median duration of UC at the time of thiopurines commencement decreased from 21 years in Group A to 2 years in Group D (P<0.0001). The proportion of subjects on thiopurines maintenance for 6-months or longer

increased through the decades (P<0.0001). Early thiopurine maintenance increased significantly over the decades from 0.7% in Group A to 2.4% in Group B, 7.7 Group C and 18.3% in Group D (p<0.0001) (Table 3.2). The median duration of thiopurine exposure in the early thiopurine maintenance group was 4 years (IQR: 2-8).

FACTORS ASSOCIATED WITH EARLY USE OF THIOPURINES

On univariate analysis, earlier thiopurine use was associated with disease extent, proctitis (ref Pancolitis) (HR: 0.35, 95%CI: 0.22-0.56, P<0.0001), younger age at diagnosis (HR: 0.98 [older compared to younger age groups], 95%CI, 0.97-0.99, P<0.0001), anti-TNF exposure (HR: 9.60, 95%CI, 6.15-14.98; P<0.0001), long-term corticosteroid exposure (HR: 5.46, 95%CI, 3.84-7.77, P<0.0001) and being diagnosed in Group D compared to Group A, B or C (P<0.0001) (Table 3.3).

On multivariate Cox proportional hazard regression analysis, younger age of diagnosis (HR:0.98, 95% CI, 0.98-0.99; P=0.002), long-term corticosteroid use (HR:5.19, 95%CI, 3.60-7.45, P<0.0001), anti-TNF exposure (HR:2.28, 95%CI, 1.43-3.64, P<0.0001) and earlier decades of diagnosis (HR: 0.03 (ref Group D), 95%CI: 0.01-0.06, P<0.0001) were associated with early use of thiopurines.

COLECTOMY RELATED TO ULCERATIVE COLITIS

A total of 116 subjects had colectomy (Supplement Table 1). Six subjects had emergency colectomy at diagnosis and 15 were for dysplasia or colorectal cancer. The probability of colectomy at 5, 10 and 20 years from diagnosis was 6.3%, 9.3% and 15.1% (Figure 3.2a). Across the 4 decades from A to D, the 10-year risk of colectomy was 9.7%, 12.8%, 7.5% and 7.8% (p=0.012) (Figure 3.2b).

FACTORS ASSOCIATED WITH COLECTOMY

All baseline characteristics and medication use were considered in the univariate analysis (Table 3.4). Long-term corticosteroids use (HR: 6.14, 95%CI: 3.72-10.16, P<0.0001), anti-TNF exposure (HR: 3.58, 95%CI: 1.65-7.74, P=0.001) and disease extent (P<0.0001) were significantly associated with time to colectomy. Early thiopurines maintenance was not significantly associated with time to colectomy (HR 0.31, 95%CI: 0.07-1.25, P=0.09).

On multivariate analysis, early thiopurines maintenance decreased the need for surgery (HR: 0.13, 95%CI: 0.03-0.55, P=0.006) (Figure 3.3). Decade of diagnosis was not associated with time to colectomy (P=0.11). Number of subjects needed to be treated to reduce one colectomy at 5 and 10 years was 18.18 (95% CI: 16.39 - 35.71) and 12.58 (95%CI: 11.22-24.81).

After propensity score matching, early thiopurine maintenance was associated with significantly reduced probability of colectomy (HR: 0.10, 95%CI: 0.03- 0.43, P=0.002).

PROXIMAL PROGRESSION OF DISEASE

A total of 30.8 % of subjects with proctitis and 13.0% of subjects with left sided colitis experienced proximal progression of disease extent during follow-up. The probability of disease extent progression at 5 and 10 years was 18.6% and 33.1% for subjects with initial diagnosis of proctitis and 6% and 11.0% for subjects with left sided colitis (P<0.0001, Figure 3.4a). Disease extent progression was associated with increased risk of colectomy (HR: 2.20, 95%CI: 1.07-4.54, P=0.032) and early maintenance of thiopurines (HR: 2.53, 95%CI: 1.47-4.34, P=0.001) using time dependent Cox regression analysis. After propensity score matching, early thiopurine maintenance was associated with reduced risk of proximal progression of disease extent (HR: 0.29, 95%CI: 0.10-0.78, P=0.015) (Figure 3.4b).

3.5 Discussion

Hospitalization and surgery are considered to be markers of more severe disease and cost-drivers in UC. Effective treatment strategies, therefore, should not only result in disease and symptom remission, but also demonstrable endpoints such as decreased need for colectomy. Thiopurines maintain remission in UC [21], promote mucosal healing [22] and decrease CD complications as well as relapses following surgery [8, 23]. Additionally, early commencement of thiopurines might help prevent intestinal damage and reduce both colectomy rates and proximal disease progression. Previously, thiopurine use was temporally linked to decreased colectomy rates [24, 25], but strategies to remove bias such as propensity score matching were not performed and confounders might be responsible for this observed relationship.

In this cohort study, thiopurines started early and maintained for >6 months were associated with a significant reduction in colectomy rate and progression of disease extent. Commencing thiopurines early before cumulative damage to the bowel might be an appropriate strategy to reduce submucosal fibrosis, which predicts the need for colectomy [11]. Fibrosis in ulcerative colitis is directly linked to severity and chronicity of mucosal inflammation. Thiopurines typically require up to 16 weeks to be efficacious [26]. Commencing and maintaining treatment earlier might reduce cumulative submucosal fibrosis that results from recurrent flares [11]. Early aggressive and 'top-down' strategies have been advocated for treatment of Crohn's disease [27]. To avoid biases of futile late introduction of thiopurines therapy, we defined early thiopurine therapy as starting within 5 years of diagnosis and maintenance for at least 6 months.

During the study period, immunomodulators were not first line maintenance therapy for UC and as such very few would start these in the first year or so. Patients often cycle through oral and per rectal mesalazine and courses of steroids before moving onto a thiopurine, unless dictated by severe uncontrolled disease. Five years was an arbitrary value that reflected more modern practice of thiopurine initiation. The median time to commencing thiopurine in the most recent 2 decades of analysis was 2 and 6 years respectively. Five years would capture sufficient subjects for analysis, consistent with practice and biologically plausible in modifying disease progression. Selecting a

shorter time frame risks too fewer participants in the early thiopurine commencement arm in order to allow for meaningful analysis.

Twelve percent of our subjects underwent colectomy during follow up, consistent with prior studies [3, 24, 28]. The need for colectomy decreased over time and paralleled an increase in the use of thiopurines from 7.2% in group A to 27% in group D. Early commencement of thiopurines was significantly associated with decreased colectomy rate (HR 0.13) on multivariate analysis and a 90% reduction of probability of colectomy using the propensity score model. Thus, to prevent one colectomy at 5 and 10 years after UC diagnosis, approximately 18 and 12 patients, respectively, need early treatment with thiopurines. Although thiopurines may cause some short and long term side effects [29], colectomy is also associated with 2-4% in-hospital mortality and 30% risk of surgical and infection complication rates [25, 30]. Colectomy can also result in diarrhea, stomal hernia and pouchitis and increase health-care cost and affect quality of life. In a previous population based study, early thiopurine maintenance resulted in a 71% reduction in the rate of colectomy compared with use for a shorter period of time [31]. Contrary to our findings, this beneficial effect was not observed in early thiopurines users defined as treatment initiation within the first year of diagnosis. The difference with our study findings could be explained in part by differing definitions of early commencement of thiopurines and that our study also required medication maintenance of 6-months or more. Commencing thiopurines in the first year of diagnosis is usually reserved for subjects with severe adverse phenotypes most likely to require subsequent surgery. Our study also excluded patients who had emergency colectomy at diagnosis, where there was no chance to use thiopurines as a maintenance agent. In our study, by correcting for all confounder variables, the propensity score matching clearly showed a beneficial effect of thiopurines in decreasing colectomy rate.

In 20.1% of patients with proctitis or left sided colitis, disease extent progressed proximally and was associated with 2.2 fold increased risk of colectomy, consistent with other studies [3]. Early thiopurine maintenance was associated with reduced risk of disease progression (71%) using

propensity score matching. A previous meta-analysis also showed azathioprine to be effective in the maintenance of remission, endoscopic improvement and mucosal healing [21].

Strengths of this study include the large sample size, long duration of follow up, and thoroughness of disease characterization at the time of diagnosis. Furthermore, meticulous monitoring and validation of data capture ensured that the timing of thiopurine initiation and medication was precisely captured. Our study method was also more robust than studies using insurance data, hospital coding or population data where patient and disease characteristics, medication dose and adherence and indication for colectomy cannot be verified with certainty. Unlike previous publications [24, 25], this study also sought to eliminate type II biases by propensity matching. Additionally, it conforms to evidence-based management and case definitions, which may not be found in insurance data, hospital coding, or de-identified data. We also used two robust and objective endpoints of disease being proximal progression of disease based on endoscopy data and colectomy.

There are limitations of this study. First, the study population was from a single geographical region and might limit generalizability. However, this was an established and well-characterized cohort across several ambulatory clinics and private rooms that had been validated against other IBD endpoints with long duration of follow up [6, 8, 14, 15]. Second, changing treatment paradigms and diagnostic methods over time may be responsible for the differences in colectomy rate. However, accounting for the decade of diagnosis in the multivariate analysis and propensity score matching excluded diagnostic era as an independent predictor for colectomy. Third, this was a cohort study and did not test the effects of thiopurines on surgery using a prospective randomized controlled trial (RCT) design. A RCT that tests thiopurine in reducing colectomy rates, however, would require a large sample size and prolonged patient-years of follow up in order to collect sufficient colectomy rates and would not be practical. The use of biological agents would confound the data. The inclusion of patients who started and maintained thiopurines after 5 years into the non-exposed arm, would have provided survival benefit to this group of patients. Finally,

our studies may underestimate the potential efficacy of thiopurines as therapeutic drug monitoring of 6-thioguanine nucleotide (6-TGN) levels were not consistently performed during the study period. Thus, our data may be an underestimation of the efficacy of thiopurines, and the true beneficial effect of thiopurines on UC patients is at least as good as those presented.

In conclusion, early thiopurine maintenance for more than 6 months within 5 years of diagnosis of UC was associated with a significant reduction in the risk of colectomy and proximal progression of disease. These findings were consistent regardless of the decade of diagnosis after propensity matching, suggesting that a drug-induced beneficial effect is seen.

Table 3.1 Demographics and patient characteristics at time of diagnosis

	Total (1970-2009)	Group A (1970-1979)	Group B (1980-1989)	Group C (1990-1999)	Group D (2000-2009)	P
No of patients	982	138	292	237	315	
Median follow up (interquartile range),yr	11 (5-20)	24 (18-34)	18 (7-24)	14 (10-17)	4 (2-7)	<0.0001
Patient-years of follow up	12879	3548	4796	3069	1466	
Gender, N (%)						0.78
Men	515 (52.4)	74 (53.6)	158 (54.1)	118 (49.8)	165 (52.4)	
Age, N(%)						0.07
Less than 16 year (A1)	56 (5.7)	12 (8.7)	21 (7.2)	14 (5.9)	9 (2.9)	
Between 17 and 40 year (A2)	575 (58.6)	72 (52.2)	165 (56.5)	149 (62.9)	189 (60.0)	
Age more than 40 years (A3)	351 (35.7)	54 (39.1)	106 (36.3)	74 (31.2)	117 (37.1)	
Disease extent, N (%)						<0.0001
Proctitis (L1)	286 (29.2)	25 (18.1)	74 (25.4)	74 (31.2)	113 (35.8)	
Left sided colitis (L2)	424 (43.2)	53 (38.4)	136 (46.7)	105 (44.3)	130 (41.3)	
Pancolitis (L3)	271 (27.6)	60 (43.5)	81 (27.8)	58 (24.5)	72 (22.9)	
Not documented	1					
Smoking status, N (%)						0.50
Current smokers	54 (10.6)	5 (18.5)	6 (9.5)	17 (11.5)	26 (9.6)	
Ex-smokers	92 (18.1)	5 (18.5)	8 (12.7)	23 (15.5)	56 (20.7)	
Never-smokers	363 (71.3)	17 (63.0)	49 (77.8)	108 (73.0)	189 (69.7)	
Not documented	473					
Extraintestinal, N(%)						0.21
Yes	154 (15.7)	23 (16.7)	35 (12.0)	43 (18.1)	53 (16.8)	
No	828 (84.3)	115 (83.3)	257 (88.0)	194 (81.9)	262 (83.2)	
Not documented	0					

Table 3.2 Drug therapy during follow-up grouped according to decade of diagnosis (N [%] within time period

	Total (1970-2009)	Group A (1970-1979)	Group B (1980-1989)	Group C (1990-1999)	Group D (2000-2009)	P
Long-term corticosteroid	372 (37.9)	59 (42.8)	124 (42.6)	90 (38.0)	99 (31.4)	0.021
Mesalazine	949 (96.6)	136 (98.6)	286 (97.9)	228 (96.2)	299 (94.9)	0.107
Anti-TNF	25 (2.5)	0 (0)	2 (0.7)	4 (1.7)	19 (6.0)	<0.0001
Thiopurines Exposure	177 (18.0)	10 (7.2)	27 (9.2)	53 (22.4)	87 (27.6)	<0.0001
thiopurines maintenance	127 (12.9)	7 (5.1%)	19 (6.5)	37 (15.6)	64 (20.4)	<0.0001
Early thiopurines	83 (8.5)	1 (0.7)	7 (2.4)	18 (7.7)	57 (18.3)	<0.0001
Median time to starting thiopurines (years, IQR)	3 (1-9)	23 (14-30)	10 (3-14)	6 (2-11)	2 (1-4)	<0.0001

Table 3.3 Factors Affecting time to Initiation of Thiopurine Therapy in UC on Cox Proportional Hazard Regression

Covariant	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Gender	0.86 (0.64-1.15)	0.31		
Age at diagnosis	0.98 (0.97-0.99)	<0.0001	0.98 (0.98-0.995)	0.002
Disease extent		<0.0001		<0.0001
Proctitis (E1)	0.35 (0.22-0.56)	<0.0001	0.37 (0.23-0.60)	<0.0001
Left-sided (E2)	0.84 (0.61-1.15)	0.28	0.72 (0.52-0.99)	0.044
Pancolitis(E3)	Reference		Reference	
Extra-intestinal	1.33 (0.93-1.91)	0.12		
Mesalazine use	5.89 (0.84-42.02)	0.08		
Long-term steroids use	5.46 (3.84-7.77)	<0.0001	5.19 (3.60-7.45)	<0.0001
Anti-TNF use	9.60 (6.15-14.98)	<0.0001	2.28 (1.43-3.64)	0.001
Decade of diagnosis		<0.0001		<0.0001
1970-1979	0.44 (0.20-0.96)	<0.0001	0.03 (0.01-0.06)	<0.0001
1980-1989	0.10 (0.06-0.17)	<0.0001	0.08 (0.05-0.13)	<0.0001
1990-1999	0.36 (0.25-0.53)	<0.0001	0.33 (0.23-0.49)	<0.0001
2000-2009	Reference			
Excluded from the model mesalazine use (p=0.28)				

Table 3.4 Factors Affecting Time to first intestinal resection on Multivariate Cox Proportional Hazard regression

Covariant	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Gender	0.79 (0.52-1.18)	0.25		
Age at diagnosis	1.0 (0.99-1.01)	0.99		
Disease extent		<0.0001		<0.0001
Proctitis (E1)	0.12 (0.06-0.25)	<0.0001	0.18 (0.09-0.40)	<0.0001
Left-sided (E2)	0.26 (0.16-0.41)	<0.0001	0.27 (0.17-0.42)	<0.0001
Pancolitis (E3)	Reference		Reference	
EIM	0.99 (0.59-1.69)	0.99		
Smoking ever	1.55 (0.76-3.17)	0.23		
Early thiopurine maintenance	0.29 (0.07-1.20)	0.09	0.13 (0.03-0.55)	0.006
Mesalazine use	1.26 (0.31-5.10)	0.75		
Long-term steroids use	6.14 (3.72-10.16)	<0.0001	4.91 (2.92-8.26)	<0.0001
Anti-TNF use	3.58 (1.65-7.74)	0.001	2.52 (1.13-5.60)	0.02
Decade of diagnosis		0.03		0.11
1970-1979	1.40 (0.65-2.98)	0.39	0.65 (0.29-1.43)	0.28
1980-1989	2.11 (1.01-4.07)	0.03	1.23 (0.62-2.42)	0.55
1990-1999	1.07 (0.51-2.25)	0.86	0.79 (0.37-1.70)	0.54
2000-2009	Reference			
EIM=extra-intestinal manifestation				

Supplement table 3.1: Types of first major abdominal surgery performed for UC at any time during follow up

Supplement Table 1. Types of first major abdominal surgery performed for UC at any time during follow up	
Procedure type	N (%)
Subtotal colectomy & ileorectal anastomosis	12 (10.3)
Total colectomy and ileostomy	63 (54.3)
Total colectomy and pouch formation	32 (27.6)
Subtotal colectomy and mucous fistula formation	1 (0.9)
Right hemicolectomy	5 (4.3)
Anterior resection	2 (1.7)
Segmental resection	1 (0.9)

Figure 3.1 Kaplan-Meier curve showing cumulative probability of Thiopurine use according to decade of diagnosis in patients with UC (p<0.0001).

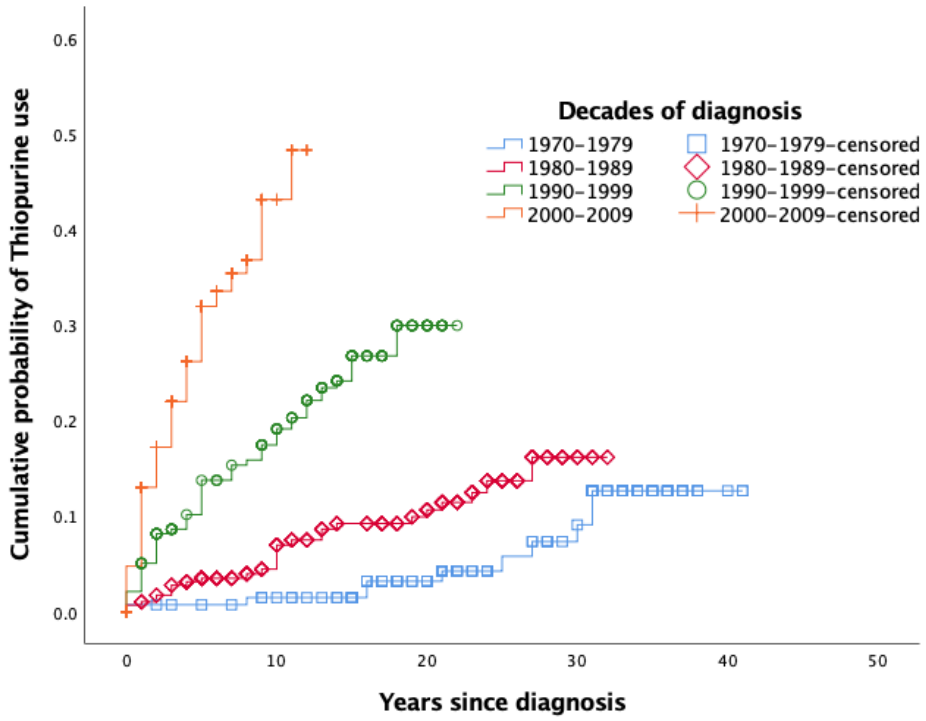
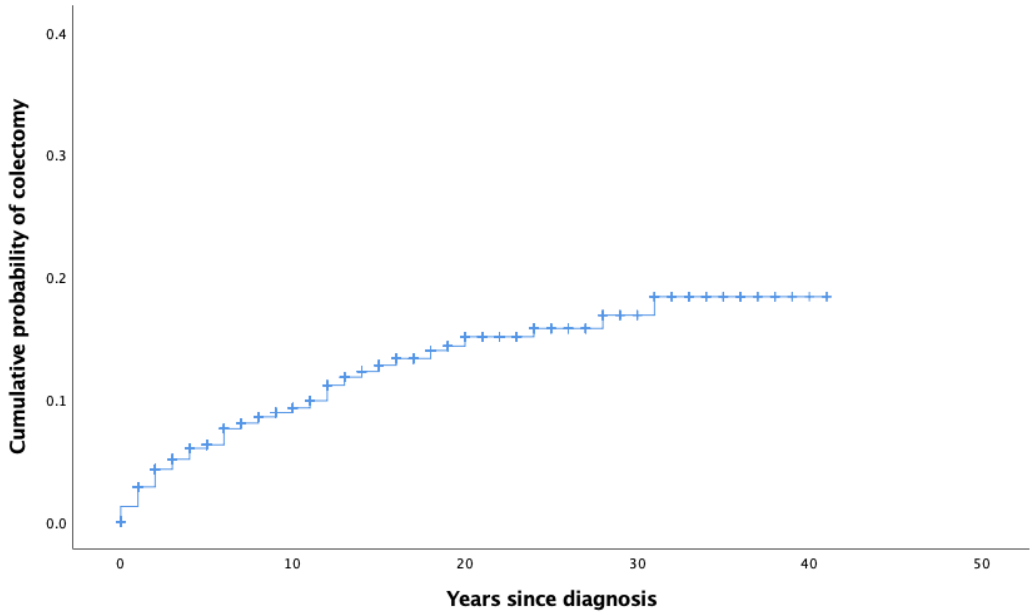


Figure 3.2 Kaplan-Meier curve showing (a) cumulative probability of colectomy, (b) in the different decades of diagnosis

(a).



(b)

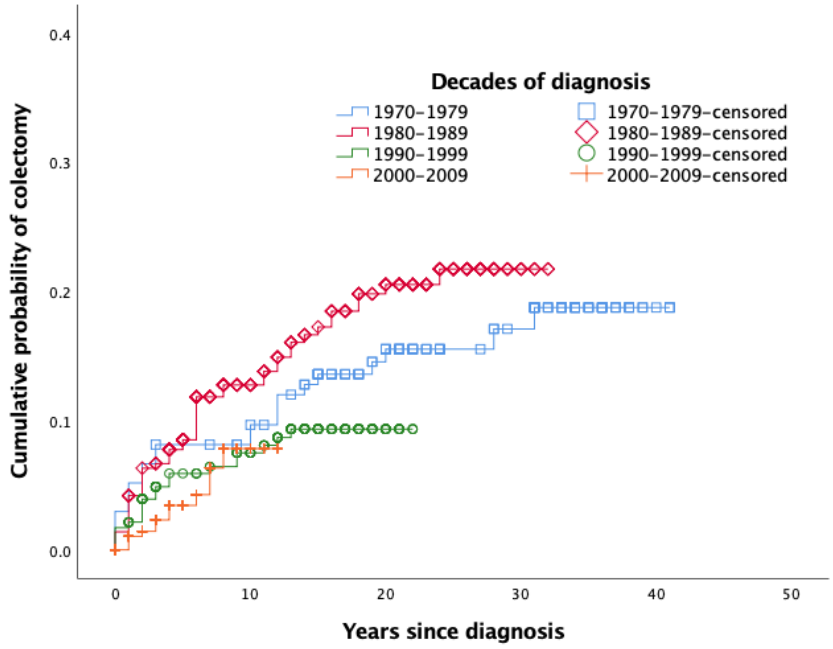


Figure 3.3 Kaplan-Meier curve showing cumulative probability of colectomy in early thiopurines maintenance after adjusting for confounders.

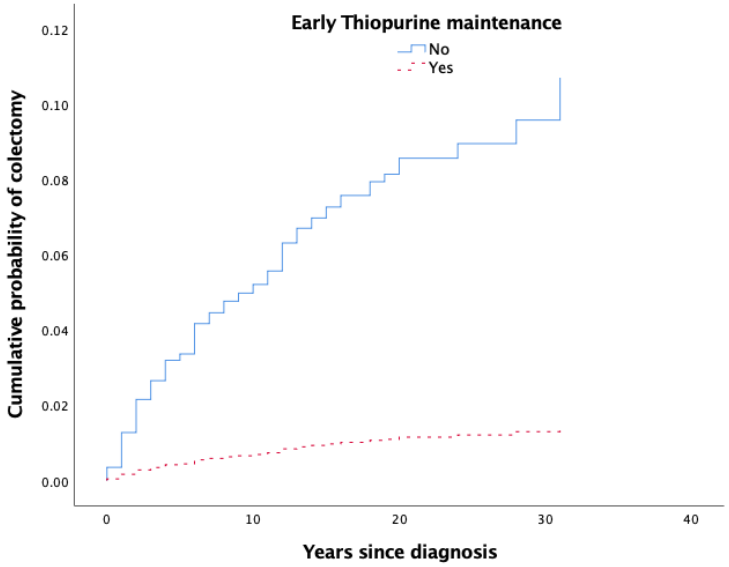
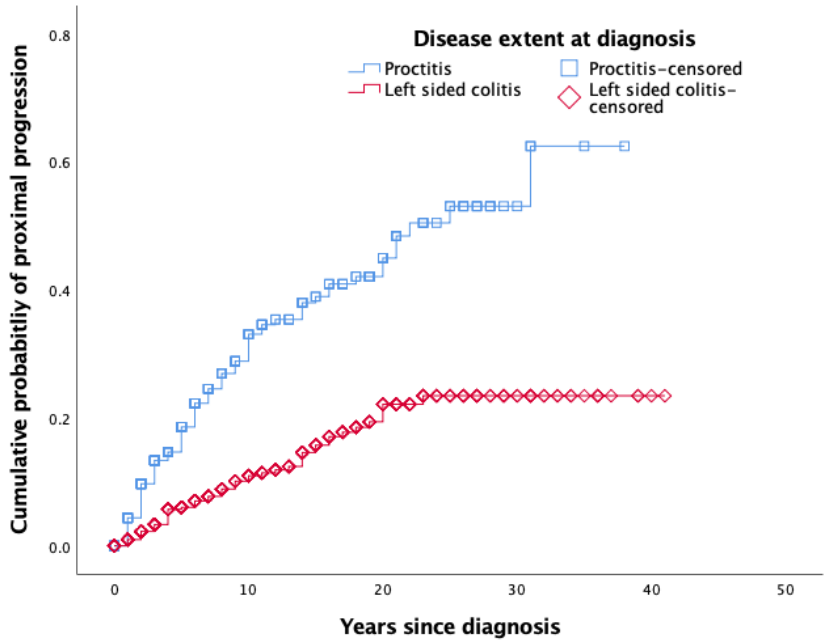
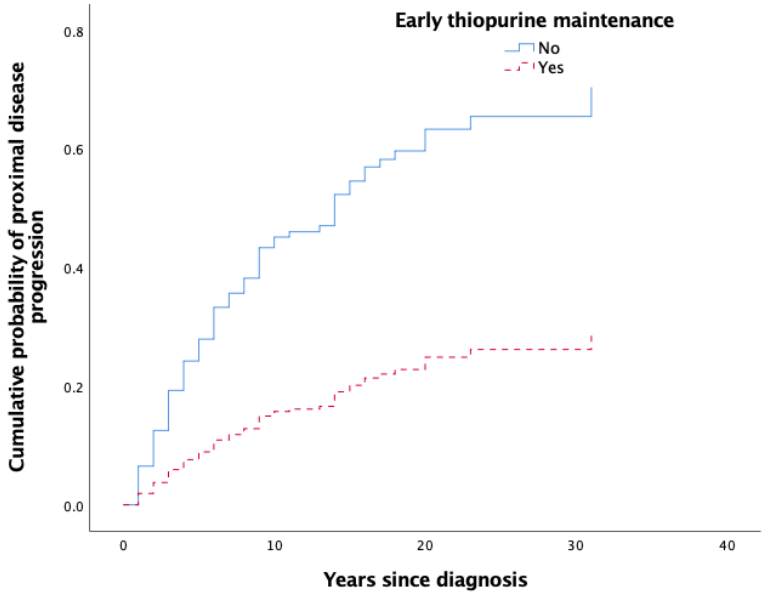


Figure 4. Kaplan-Meier curve showing cumulative probability of disease progression (a) according to the extent of disease on diagnosis and (b) with early thiopurines maintenance after adjusting for confounders.

(a)



(b)



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CHAPTER 4 (STUDY 3) IMPACT OF CONCOMITANT USE OF THIOPURINES, ON THE CLINICAL RESPONSES AND TIME TO FAILURE OF ADALIMUMAB

This chapter is presented as a published journal article, “Thiopurines Dosed to a Therapeutic 6-Thioguanine Level in Combination with Adalimumab Are More Effective Than Subtherapeutic Thiopurine-based Combination Therapy or Adalimumab Monotherapy During Induction and Maintenance in Patients with Long-standing Crohn’s Disease” in manuscript format

Thiopurines dosed to a therapeutic 6-thioguanine level in combination with adalimumab is more effective than sub-therapeutic thiopurine based combination therapy or adalimumab monotherapy during induction and maintenance in patients with long standing Crohn's disease.

(Short title: Combination therapy with thiopurine and adalimumab in Crohn's Disease)

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Non-standard Abbreviations:

CIM: concomitant immunomodulation

ADA: adalimumab

TGN: thioguanine nucleotides

IFX: infliximab

MTX: Methotrexate

AZA: azathioprine

MP: mercaptopurine

TPMT: thiopurine-S-methyltransferase

MeMP: methylated metabolites

CRP: C reactive protein

Conference presentations:

Digestive Disease week 2014 – Oral presentation

Australian Gastroenterology Week 2013 – Oral presentation

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4.1 Abstract

Background and aims

The benefit of concomitant immunomodulation (CIM) with adalimumab (ADA) in Crohn's disease is poorly understood. We aimed to compare ADA monotherapy with combination therapy with thiopurines, stratified by thioguanine nucleotides (TGNs).

Methods

Retrospective observational study of ADA induction and maintenance. Thiopurines were classified according to TGNs (>235 pmol/8x10^8RBC therapeutic).

Results

At induction, response was more frequent in combination than ADA monotherapy (83 vs 61%, p = 0.02) and with therapeutic compared to sub-therapeutic TGNs (87 vs 70% p = 0.011). Amongst 280 maintenance semesters in 91 patients; remission was higher with combination than monotherapy (81 vs 60%, p < 0.0001) and therapeutic vs sub-therapeutic TGNs (85 vs 58%, p = 0.004). Therapeutic TGN (OR 4.32, 95% CI: 1.41–13.29, p = 0.01) and albumin (OR 1.09, 95% CI: 1.01–1.18, p = 0.03) were predictors of response to induction. Therapeutic TGN (OR 3.71, 95% CI: 1.87–7.34, p < 0.0001) and ileal disease (OR 0.21, 95% CI: 0.08–0.57, p = 0.002) were predictors of remission semesters. CIM at induction was associated with longer time to failure (69 vs 36 months, p = 0.009). Therapeutic TGN at induction (p = 0.03) and male gender (p = 0.026) were associated with time to failure.

CONCLUSION

Combination therapy was superior to ADA monotherapy for induction and during maintenance. This benefit was increased further when thiopurines resulted in therapeutic TGNs. Early use of adequately dosed thiopurines (≥3 months prior to starting ADA) was associated with improved clinical outcomes.

Keywords: Crohn's disease, thiopurine, combination therapy, adalimumab

4.2 INTRODUCTION

Adalimumab, (ADA, Humira, Abbott Laboratories, Abbott Park, IL) a fully humanized monoclonal IgG antibody directed against tumor necrosis factor alpha, is effective at inducing and maintaining remission in patients with moderate-to-severe Crohn's disease.[1-5] However, a proportion of patients fail to respond to ADA. Of those that do respond, approximately 30% lose response by 12 months, with a further 10% losing response annually thereafter.[5-7] Accordingly, there is a need to understand whether there are factors that are associated with response and loss of response to improve outcomes.

Immunogenicity is a well-recognized mechanism implicated in ADA failure[8]. Antibodies to ADA have been shown to influence the pharmacokinetics of ADA, leading to increased drug clearance and lower ADA levels.[9] The use of concomitant immunomodulation, (CIM) with anti-TNF agents decreases anti-drug antibody formation.[10-12] In the case of infliximab, (IFX) combination therapy is superior to monotherapy, both for patients with Crohn's disease and those with ulcerative colitis UC.[11-13] However, there is less evidence for a similar effect with ADA. A recently published prospective open-label study of 176 treatment naïve patients with moderate to severe CD randomized to ADA monotherapy compared to combination therapy with azathioprine found no difference in rates of clinical remission at week 26[14]. Further, there were no differences in the proportion of patients meeting the primary endpoint when patients were stratified according to week 12 thioguanine nucleotide threshold of 250pmol/8 x 10^8 red blood cell (RBC), ($p = 0.13$). However, they found significantly higher endoscopic remission at week 26 in the combination group, indicating likely benefit of combination therapy. Further evidence regarding the need for CIM when using ADA is based on sub-analysis of randomized controlled trials and retrospective studies.[8,15] The results of these studies are conflicting, suggesting that further data would be of use. Studies assessing whether the intensity of CIM, (in the case of thiopurines measured using 6-thioguainine nucleotide metabolites (TGN)) is of importance are lacking, an area recently addressed in two IFX-treated cohorts.[16,17]

The aim of this study was, therefore, to investigate the influence of CIM on clinical outcomes in a well characterized and prospectively assessed cohort of Crohn's disease patients treated with ADA. In addition, we aimed to assess whether therapeutic TGN concentrations were associated with improved outcomes compared with sub-therapeutic TGNs in patients on thiopurine combination therapy.

4.3 METHODS

STUDY DESIGN

We performed a retrospective single-centre cohort study of consecutive patients with moderate-to-severe Crohn's disease, who commenced ADA at Guy's and St. Thomas' Inflammatory Bowel Disease Centre between January 2006 and June 2013.

STUDY POPULATION

The diagnosis of Crohn's disease was based on standard endoscopic, histological and radiological criteria.[18] Only patients who commenced ADA at our centre were included. Data were collected prospectively from January 2009 through our Virtual Biologic Clinic which has been described previously.[19] Within this setting, patients are reviewed prior to commencing ADA and subsequently every 3-6 months, unless indicated earlier. All other data were retrieved from the electronic patient record.

Thiopurines (azathioprine (AZA), mercaptopurine (MP) and thioguanine) or Methotrexate (MTX) were commenced at the treating physician's discretion. AZA and MP were initially dosed according

to body weight (2-2.5mg/kg AZA, 1-1.5mg/kg MP) after measurement of thiopurine-S-methyltransferase (TPMT) activity[20-22] with dose reduction by 50% in TPMT heterozygotes.[23] We routinely measure thiopurine metabolites in all patients (TGN and methylated metabolites)[24] four weeks after starting therapy to guide dose adjustment; a TGN of 230-450 pmol/8x10^{8}RBC is considered therapeutic.[25] Patients with sub-therapeutic TGNs, evidence of hepatotoxicity or intolerance in conjunction with a metabolite profile consistent with hypermethylation, (defined as methylated metabolites to TGN ratio > 11:1) were changed to allopurinol 100mg co-prescription with thiopurine dose reduction to 25-33% of the original dose.[26] During maintenance TGNs are routinely performed in patients every 6-12 months. MTX was dosed at 15-25mg weekly orally with folic acid supplementation[27] and thioguanine at 20-40mg daily.

Biologics were started as a step-up therapy in patients who either failed or intolerant of immunomodulators. ADA was initiated as the first line biologic or after failure of IFX. All patients initiated ADA at standard induction dosing, (160mg/80mg weeks 0 and 2) followed by maintenance (40mg every other week). In those with an incomplete response after induction or secondary loss of response, ADA was intensified to 40mg each week. Dose reduction back to 40mg every other week was considered after attainment of remission, based on a combination of clinical, biochemical, endoscopic and radiological parameters.

ASSESSMENT OF RESPONSE – INDUCTION

Response to induction was assessed at 12 weeks by physician global assessment after consideration of clinical activity, (Harvey-Bradshaw Index[28] (HBI)) biomarkers (C-reactive protein, (CRP), faecal calprotectin) and imaging or endoscopy, where available. HBI of <4 , CRP < 5 mg/L and calprotectin <50 mg/g were considered as markers of response. Patient response was assessed and documented by at least 2 or more experienced IBD physicians after considering all available parameters.

Patients maintained on a stable dose of immunomodulator ≥ 3 months prior to ADA induction and who continued for a ≥ 6 months after induction were defined as CIM at induction. All other patients were classified as not being on CIM at induction. Patients taking thiopurines were further classified according to TGN levels; > 235 was considered therapeutic.

ASSESSMENT OF RESPONSE – MAINTENANCE

Beginning after the first 12 months of treatment, patients were assessed for long-term clinical response, per 6-monthly semesters. Semesters with ≥ 3 months of CIM therapy were considered CIM semesters. Patients on thiopurines were again stratified according to TGNs measured from each semester, where available.

Semesters were classified per one of three definitions:

Flare semester: active clinical disease resulting in treatment intensification (ADA dose escalation, new corticosteroids or addition of CIM), hospital admission due to active Crohn's disease, new perianal disease or Crohn's disease-related surgery not leading to ADA withdrawal.

Remission semester: semester without a flare either on every other week or weekly dosing.

Failure semester: Failure, defined as withdrawal of ADA due to primary non-response, secondary loss of response despite dose-intensification, or due to development of adverse effects or complications.

FACTORS ASSOCIATED WITH CLINICAL RESPONSE

Covariates that were assessed for response to induction, ADA failure, dose intensification and semester outcomes included: gender, disease duration, age at diagnosis, disease location and behaviour as per Montreal classification[29], smoking status, weight, previous anti-TNF exposure,

previous surgery, CIM 3 ≥ months prior to starting therapy, CIM status during semester, and CRP and Harvey-Bradshaw Index at commencing ADA. Interactions between weight and need for ADA dose intensification were also explored.

STATISTICAL ANALYSIS

Categorical variables are presented as number and percentage, and quantitative data as mean with standard deviation or median with interquartile range, as appropriate. Between group comparisons were performed using Pearson's Chi-squared, independent sample t-test, or Mann–Whitney U test. Multivariate analysis was performed using Cox regression for time to failure and binary logistic regression for factors associated with induction outcome, dose escalation and semesters of remission. Covariates identified *a priori* with $p < 0.1$ on univariate analysis were entered into a multivariate backward stepwise model. Variables with $p < 0.05$ were retained in the final model and reported as adjusted hazard ratios (HRs) in the Cox regression and odds ratios (ORs) in logistic regression with 95% confidence intervals (CIs). Time to ADA failure was calculated using Kaplan-Meir survival analysis and comparisons between groups were made using the log-rank test. Two-sided P-values < 0.05 were considered significant. Statistical analyses were carried out using SPSS v23.0 (SPSS Inc., Chicago, IL).

ETHICAL CONSIDERATION

According to the guidelines of the U.K. Health Research Authority as the data collected were done so as part of routine clinical care and were evaluated retrospectively, ethical approval was not required.[30]

4.4 RESULTS

PATIENT CHARACTERISTICS

156 patients commenced ADA between January 2006 and June 2013; 123 met inclusion criteria for the induction analysis (Figure 4.1). Patient characteristics are shown in Table 4.1. CIM was prescribed for ≥ 3 months prior to starting ADA in 77/123 (63%); thiopurines were used in 67/77, MTX in 6, thioguanine in 3 and mycophenolate mofetil in 1. 57 and 59% of patients had previously been exposed to anti-TNF in the CIM, and no CIM cohorts, respectively. No significant differences in baseline CRP, ($p = 0.49$), albumin ($p = 0.19$) or Harvey-Bradshaw Index ($p = 0.052$) were observed between CIM and no-CIM groups. Follow-up was similar in both groups (20 vs 22 months, $p = 0.4$)

280 semesters amongst 91 patients were available for the maintenance analysis; 201 (72%) were classified as CIM semesters (143 with immunomodulators ≥ 3 months prior to starting ADA vs. 58 who were not) compared with 79 (28%) ADA monotherapy semesters (20 in patients treated with immunomodulators ≥ 3 months prior to starting ADA vs. 59 who were not) ($p < 0.001$). Thiopurines were used in 84% of semesters, of these TGNs were available in 92%. 135 (88%) were therapeutic and 19 (12%) sub-therapeutic.

PRIMARY RESPONSE

Complete response was seen in 92/123 (75%) at week 12; The mean CRP improved from 18.8 mg/L to 4.4 mg/L and the HBI from 7.5 to 1.6 (Supplement 1a). Among complete responders' clinical remission with HBI ≤ 4 was seen among 92% and biochemical remission with CRP normalization (<5mg/L) in 84%. A total of 76.5% achieved both clinical and biochemical remission (Supplement 1b). The rate of primary non-response was significantly lower among patients treated with CIM

(12 vs 30%, p = 0.02) (Figure 4.2). In addition, complete response was also higher amongst those treated with CIM compared to those not treated with CIM (83 vs 61%, p = 0.02).

Most, (97%) patients treated with thiopurines had TGNs measured prior to starting ADA; 16% were sub-therapeutic. Response to induction was seen in 48 (87%), 7 (70%) and 28 (61%) of those with therapeutic TGNs, sub-therapeutic TGNs and no CIM, respectively (p = 0.011) (Figure 4.3).

In univariate analysis CIM use at induction and serum albumin were significantly associated with response at week 12 (Table 4.2). On multivariate analysis, therapeutic TGN levels (OR 4.32, 95% CI: 1.41-13.29, p = 0.01) and albumin level (OR 1.09, 95% CI: 1.01-1.18, p = 0.03) were independent predictors of response to induction. (Table 4.2).

SEMESTER ANALYSIS

Of 280 semesters, every other week dosing was observed in 200 (72%) and weekly in 80 (29%). A similar proportion of CIM and non-CIM semesters were observed in each dosing regimen (every other week 74 vs weekly 68%, p = 0.31). More CIM semesters were classified as remission compared to non-CIM semesters (81 vs 60%, p < 0.0001, Figure 4.3). Considering CIM semesters, patients with therapeutic TGNs were more likely to be in remission compared to those with sub-therapeutic TGNs (86 vs 58%, p = 0.004) (Figure 4.4.)

In univariate analysis, ileal location (p = 0.001), extra-intestinal manifestations of disease (p = 0.03, and semesters with therapeutic TGNs (p < 0.0001) were associated with remission (Table 4.3). These covariates remained significant after multivariate analysis (ileal disease location: OR 0.21, 95%CI: 0.08-0.57, p = 0.002, therapeutic TGN: OR 3.71 95% CI: 1.87-7.34, p < 0.0001).

FACTORS ASSOCIATED WITH ADA FAILURE

35/123 (29%) ceased ADA during the study; 5/35 withdrew due to sustained clinical remission. A further 2/35 prescribed ADA to down-stage inflammation pre-operatively were not continued post-operatively. Hence, 28 patients were subsequently analyzed with regards to ADA failure. Mean time to failure was 58 months (95% CI: 50.5–66.3). CIM ≥ 3 months prior to ADA was associated with longer time to failure compared to those not treated with CIM (68.5 vs 35.7 months, $p = 0.009_{\text{log rank}}$) (Figure 4.5)

On univariate analysis, male gender ($p = 0.033$) and therapeutic TGN ($p = 0.03$) were associated with time to failure (Table 4.4). Therapeutic TGN ≥ 3 months prior to ADA (HR 0.37, 95%CI: 0.15–0.89, $p = 0.026$) and male gender (HR 0.39, 95% CI: 0.17–0.91, $p = 0.028$) were independently associated with time to failure on Cox regression analysis. Dose escalation did not predict subsequent ADA failure ($p = 0.20$). CIM ≥ 3 months prior to ADA was independently associated with time to failure (HR 0.37, 95% CI 0.17–0.81, $p = 0.012$).

DOSE ESCALATION AND FACTORS ASSOCIATED WITH DOSE ESCALATION

ADA was escalated to weekly dosing in 34/123 (28%) patients. Mean time to dose escalation was 12.5 months (SD 8.7). All base line characteristics were considered for univariate analysis (Supplement 2). On multivariate analysis CIM ≥ 3 months prior to starting adalimumab was not associated with time to dose escalation (HR 0.55, 95%CI: 0.28-1.09, $p = 0.088$). Baseline CRP (HR 1.01, 95% CI 1.001–1.024, $p = 0.035$) and 5-ASA treatment at ADA initiation (HR 3.97, 95%CI 1.68–9.40, $p = 0.002$) were significant independent predictors associated with time to dose escalation on multivariate analysis.

ADVERSE EVENTS

Serious adverse events occurred in 5 patients during the study. 2 malignancies occurred; metastatic breast cancer after 19 months of combination treatment with thioguanine and ADA and transitional cell carcinoma of the bladder after 27 months of ADA monotherapy. A 25-year-old male treated with thioguanine and ADA developed primary EBV infection and recovered after discontinuing both drugs. Two patients developed intra-abdominal sepsis, 4 and 10 months into treatment; one was on ADA monotherapy, the other on combination therapy with azathioprine.

4.5 DISCUSSION

We have demonstrated that in patients with Crohn's disease starting ADA, combination therapy with an immunomodulator was associated with higher rates of clinical response after induction compared to ADA monotherapy, and observed lower rates of subsequent ADA failure. During maintenance, combination therapy was associated with a decrease in the proportion of flare semesters. We assessed the relationship of thiopurines stratified according to TGN levels, not previously reported in the literature, and found that sub-therapeutic TGNs at induction and during maintenance therapy were associated with worse clinical outcomes and an increased risk of ADA failure compared to patients with therapeutic TGNs.

The situation regarding combination therapy in patients taking infliximab has been studied extensively. In a retrospective analysis of 584 semesters amongst 121 patients with IBD, Sokol et al found a significantly decreased incidence of flares (32 vs 19%), perianal complications (12 vs 4%), and mean CRP (11 vs 9%) in those treated with combination therapy compared with infliximab monotherapy.[31] Many of the patients in this cohort started infliximab upon failure of immunomodulator therapy and continued CIM after initiating infliximab, suggesting that there is a benefit of combination therapy in all patients starting IFX, not just those naïve to immunomodulators. This has also been supported by a recent meta-analyses of patient level data

in the biologic registration trials.[32] In addition, combination therapy has been shown to improve rates of deep remission, (defined as clinical remission together with normalization of CRP and mucosal healing) compared to infliximab monotherapy in patients who were previously naïve to both drugs (65 vs 25%, p = 0.037).[17]

Although the benefits of combination therapy with infliximab appear robust, evidence to support the same benefit with ADA is relatively sparse. The same meta-analysis of randomized controlled trials demonstrating a benefit of combination therapy in induction of clinical remission at 6 months with IFX, found no such association for combination therapy with ADA (OR 0.88, 95%CI: 0.58–1.35).[32] A recent prospective study randomizing treatment naïve patients with moderate-to-severe Crohn's disease to either ADA monotherapy, or combination therapy with a thiopurine found no difference in clinical remission at week 26 between the two treatment arms (72 vs 68%) although an improvement in endoscopic activity at week 26 and higher ADA trough levels were observed in those treated with combination therapy.[14]

Conversely, a recent meta-analysis amongst patients with CD found that ADA monotherapy was slightly inferior to combination therapy for induction of remission (OR 0.78, 95%CI: 0.64–0.96, p= 0.02) although no such benefit was seen for maintenance of clinical remission (OR 1.08, 95% CI: 0.79–1.48, p = 0.48) nor was combination therapy superior to monotherapy in terms of need for dose escalation (OR 1.13, 95%CI: 0.69–1.85, p = 0.62).[33]

Our study builds on previously published open data. A retrospective study from two large centres described 207 patients with Crohn's disease and found that CIM maintained for 3 months or more within 6 months of initiating ADA was associated with a lower risk of ADA failure and fewer flare semesters during maintenance.[15] CIM was not, however, associated with improved rates of response to induction therapy, nor was ongoing CIM associated with fewer semesters of flare nor with a lower risk of ADA failure. Semesters in which ADA was dosed weekly, rather than every other week, were classified as flares, even if the patient remained well during the semester, which may have influenced these results. It is recognized that secondary loss of response occurs in a significant proportion of patients during ADA maintenance and that dose escalation can recapture response in many.[6] It is possible to argue that patients who regain response on dose escalation

and remain well on weekly dosing are, therefore, not treatment failures but, rather, represent a subgroup of patients who require higher dosing to achieve therapeutic drug levels to maintain remission.[34] In the current study, therefore, a semester requiring dose escalation was classified as a flare; subsequent semesters were classified according to clinical status and were not automatically recorded as flare semesters based on the need for weekly dosing. Interestingly, dose escalation was not associated with time to failure, supporting our study design.

For the first time, we report the association between adequate dosing of thiopurines (TGN > 235 pmol/8x10^{8}RBC) and clinical response. We found significantly higher response rates in patients with therapeutic compared with sub-therapeutic TGNs at both induction (88 vs 70%) and during maintenance (85 vs 58%). In this regard, data are beginning to emerge demonstrating that the intensity of concomitant immunomodulation influences the pharmacokinetics of anti-TNF therapy and subsequent clinical outcomes. A Dutch group found that MTX reduced immunogenicity to IFX in a dose-dependent manner, with the odds of developing anti-drug antibodies being 0.36 (95% CI: 0.18–0.74) in the 5-10mg/week, 0.22 (95% CI: 0.10–0.46) in the 12.5-20mg/week and 0.14 (95% CI 0.07–0.28) in patients on >22.5mg/week) relative to patients not treated with MTX.[35] In addition, in a post-hoc analysis of the SONIC study, patients on combination therapy with azathioprine with an increase of 7 femtoliters in the mean corpuscular volume (delta MCV), used as a surrogate marker for therapeutic TGN levels, were more likely to achieve mucosal healing (75 vs 47% for delta MCV >7, p = 0.017) and maintain therapeutic trough infliximab levels > 3 µg/mL at week 30 (68 vs 39% for delta MCV >7, p = 0.003).[36] Similarly, in a cross-sectional analysis of 72 patients with inflammatory bowel disease, IFX drug levels were higher amongst those on combination therapy with a thiopurine compared with IFX monotherapy (13 vs 4.8 µg/mL,) and a TGN cut-off of 125 pmol/8x10^{8}RBC best predicted a significantly higher IFX trough level.[16] Taken together with the findings that higher anti-TNF drug levels are associated with improved rates of remission[37,38] these findings suggest that the dose of thiopurine may be of significant importance.

A recent Australia New Zealand Consortium cohort study comparing IFX/ADA with or without IM suggested that corticosteroids used at induction or in the preceding 12 months was associated with 9-13 times greater risk of flare semester during maintenance[39]. There was significantly higher

use of steroids at induction in the none-CIM arm in the current cohort. However, most of these patients were either intolerant of or failed IM therapy and steroids were used as a bridge to biologic therapy. Additionally there was no difference in steroid use between patents with therapeutic and sub-therapeutic TGN levels at induction (21.8% vs 37.5%, p=0.07).

The utility of measuring TGN in patients taking thiopurines as combination therapy is perhaps even greater when one considers rates of non-adherence and the impact of hypermethylation. Adherence to thiopurines is a well-recognized problem in inflammatory bowel disease.[40] Similarly, under dosing with thiopurines has been reported in 29% when weight based dosing is employed.[24] Thiopurine hypermethylation, whereby shunting occurs away from the therapeutic TGNs towards a methylated metabolite profile, is seen in 15-20% and is associated with an inability to achieve therapeutic TGN.[41] Without thiopurine metabolite testing a large proportion of patients will fail to achieve a therapeutic TGN; the structured approach to optimisation of thiopurines in our cohort may explain why a greater benefit of CIM was observed compared with other cohorts.

The development of antibodies against ADA has been implicated as a mechanism leading to secondary loss of response and treatment failure.[42,43] Combination therapy can improve the pharmacokinetics of infliximab by increasing drug levels[44] and by decreasing anti-infliximab antibody production (RR: 0.50, 95% CI: 0.42 – 0.59, p < 0.00001).[44] A recent study demonstrated the beneficial effect of concomitant thiopurine in reducing immunogenicity, regardless of previous clinical response to thiopurines[45]. In a retrospective analysis of 536 samples collected from 148 patients analyzed using a drug tolerant homogenous mobility shift assay, antibodies to ADA were detected in 20% after a median of 34 weeks[8]. CIM was associated with decreased antibody formation (HR: 0.23, 95% CI: 0.06–0.86) and antibodies were associated with future elevated CRP (p = 0.0013) and discontinuation of ADA due to loss of response (OR 3.04, 95%CI: 1.039–9.093). Such immunogenicity occurs early during ADA therapy. A prospective observational cohort study of 272 patients treated with ADA for rheumatoid arthritis found antibodies to ADA in 28% over a 3 year follow-up; in 67% antibodies occurred within the first 28 weeks of therapy.[46] Similarly, antibodies to IFX have also been found to occur early. In a prospective observational study of 125

patients with IBD, anti-drug antibodies occurred in 46% at a median time of 1.5 months (IQR 0.5–5.5); 90% developed within 12 months and anti-drug antibody free survival was longer in patients taking combination therapy compared with IFX monotherapy (p = 0.003).[47] These findings suggest that early concomitant immunomodulation, perhaps even prior to starting anti-TNF therapy is important, as has previously been shown in murine models.[48] Thiopurines have a slow onset of action, with a mean time to response of 3.1 months.[21] Therefore, it is possible that some of the beneficial effects of combination therapy may be greater in those patients who are established on therapy prior to starting ADA.

Given the findings from our study (and some others) that early combination therapy is beneficial, and that immunogenicity occurs largely in the first 12 months of ADA therapy, a key question is whether combination therapy should be continued during maintenance. Such a decision must weigh up the benefits and risks of continued combination therapy against withdrawal to ADA monotherapy. In this regard, we demonstrated higher rates of remission semesters in those treated with CIM vs ADA monotherapy (81 vs 60%) and in those with therapeutic compared with non-therapeutic TGNs (85 vs 58%). Further, CIM use during a semester was an independent predictor of remission (OR 2.92, 95% CI: 1.62–5.25, p < 0.0001). Our results are in agreement with those from the Oxford/Liege cohort, where combination therapy beyond 6 months was associated with fewer semesters with flares (14 vs 36%, p = 0.02, OR = 0.31).[15] Recent studies have called into question the benefit of continued concomitant immunomodulation during maintenance therapy, suggesting that a lower dose of thiopurine may be equally efficacious as full weight-based dosing.[49] We were unable to explore this association in the current study as only a small proportion of patients (3/65) were found to have TGNs <125. The benefits of combination therapy must, of course, be balanced with the risks particularly in light of recent safety signals regarding the use of thiopurines.[50,51]

We acknowledge several limitations with the study. First patients were not randomized to combination therapy or ADA monotherapy, hence despite the groups being similarly matched in terms of phenotype, previous anti-TNF exposure and disease severity they are not directly

comparable. As we did not measure ADA drug levels or antibodies to ADA we cannot prove that the benefit seen with CIM was due to improvements in ADA pharmacokinetics and reductions in immunogenicity. Third, assessment of response to induction and during maintenance was made using a combination of Harvey-Bradshaw Index, CRP and fecal calprotectin. Fourth, a relatively high number of patients were treated with corticosteroids during induction (53%) which may contribute to the relatively high response rate seen overall (75%). However, there was no difference in corticosteroid use in patients who had therapeutic and sub-therapeutic levels of TGN. Finally, a relatively small proportion of patients had sub-therapeutic TGNs during induction (15%) and maintenance (12%), hence the conclusion that response rates are superior with therapeutic compared with sub-therapeutic TGNs should be interpreted with caution until it has been confirmed in other cohorts. We acknowledge that this distribution of TGNs limited our ability to apply further relevant statistical methodology such as a quartile or ROC analysis.

CONCLUSION

Combination therapy was found to be superior to ADA monotherapy in this cohort of patients with moderate-to-severe Crohn's disease with improved response at induction, more semesters in remission and a longer time to ADA failure. Further, adequately dosed thiopurines when used as concomitant immunomodulation was associated with improved clinical outcomes. We propose that, after carefully balancing the risk and benefit and noting the association of increased risks of lymphoma, non-melanoma skin cancer and possibly other malignancies,[50] immunomodulators should be initiated early when considering ADA therapy, dosed to a TGN > 235, and continued during maintenance therapy. Further randomized controlled studies are needed that incorporate thiopurine metabolite testing during both induction and maintenance.

Table 4.1 Baseline characteristics at adalimumab (ADA) initiation (n = 123)

Characteristic	CIM (n = 77)	No CIM (n = 46)	p value
Male, number (%)	40 (51.9)	25 (54.3)	0.79
Age at diagnosis, median (IQR)	21 (17-28)	22 (18-29)	0.32
Disease duration years, median (IQR)	11 (4.5-16)	9 (3.5-17.2)	0.46
Location L1:L2:L3 (%)	15.6; 19.5; 64.9	10.9; 28.3; 60.9	0.46
Upper GI involvement (%)	16.9	19.6	0.71
Behavior B1:B2:B3 (%)	36.4; 44.2; 19.4	37.0; 43.5; 19.5	0.99
Perianal disease (%)	31.2	41.3	0.25
EIM (%)	19.7	21.7	0.79
Weight kg, median (IQR)	66.0 (54.4-78.9)	69.5 (59.5-83.5)	0.35
Current smoker (%)	10.6	22.0	0.28
Family history (no:1st deg:other) (%)	90.3; 6.5; 3.2	84.6; 12.8; 2.6	0.54
Prior surgery, number (%)	41(53.2)	18 (39.1)	0.13
Perianal surgery, number (%)	13 (16.9)	7 (15.2)	0.81
Steroids at ADA induction (%)	19.5	41.3	0.01
5-ASA (%)	6.5	17.4	0.06
Prior anti-TNF exposure (%) IFX/ADA/both (%)	55.8 50.0; 2.6; 3.9	58.7 45.7; 2.2; 10.9	0.76 0.52
CRP mg/L mean (SD)	20.7 (28.5)	25.1 (30.3)	0.49
Albumin (g/L) mean (SD)	42.3 (6.6)	42.0 (4.1)	0.20
HBI, mean (SD)	7.1 (4.4)	9.0 (4.5)	0.05
CIM: concomitant immunomodulation, ADA: adalimumab, EIM: extra-intestinal manifestation, CRP: c-reactive protein, HBI: Harvey-Bradshaw Index, SD: standard deviation, IQR: interquartile range			

Table 4.2 Univariate and multivariate predictors of response at week 12

Covariant	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Gender	0.51 (0.20-1.28)	0.15		
Age at diagnosis	1.02 (0.97-1.08)	0.46		
Disease duration at start of ADA	1.00 (0.95-1.05)	0.99		
Montreal location (reference L3) L1 L2	 0.65 (0.18-2.31) 0.73 (0.25-2.16)	 0.51 0.57		
Montreal location L4	1.04 (0.32-3.43)	0.94		
Montreal behaviour (reference B3) B1 B2	 1.22 (0.35-4.23) 1.16 (0.35-3.85)	 0.76 0.81		
EIM	1.91 (0.52-7.00)	0.33		
Weight (kg)	1.02 (0.98-1.05)	0.31		
Current smoker	0.83 (0.45-1.54)	0.55		
Family history of IBD	1.39 (0.36-5.33)	0.63		
Prior bowel resection	1.01 (0.41-2.49)	0.98		
Exposure to anti-TNF	1.02 (0.41-2.54)	0.97		
Steroids at induction	0.66 (0.25-1.73)	0.39		
5-ASA at induction	0.74 (0.19-2.94)	0.67		
CIM (reference no CIM) Sub-therapeutic TGN Therapeutic TGN	 3.94 (0.45-34.12) 3.57 (1.24-10.26)	 0.21 0.18	 3.36 (0.38-29.79) 4.32 (1.41-13.29)	 0.28 0.01
CRP at induction	0.99 (0.98-1.00)	0.09	Removed	0.35
Albumin at induction	1.08 (1.01-1.17)	0.03	1.09 (1.01-1.18)	0.03
HBI at induction	0.95 (0.86-1.05)	0.95		

ADA = adalimumab, EIM = extra-intestinal manifestation, IBD = inflammatory bowel disease, CIM = concomitant immunomodulation, TGN = thioguanine nucleotide, CRP = c-reactive protein, HBI = Harvey-Bradshaw Index

Table 4.3 Univariate and multivariate predictors of remission semesters

Covariant	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Gender	1.69 (0.97-2.95)	0.06	1.77 (0.91-3.44)	0.09
Age at diagnosis	0.99 (0.97-1.02)	0.72		
Disease duration at start of ADA	1.03 (0.99-1.07)	0.09	Removed	0.26
Montreal location (reference L3) L1 L2	 0.25 (0.11-0.56) 0.57 (0.29-1.09)	 0.001 0.09	 0.21 (0.08-0.57) 0.50 (0.24-1.04)	 0.002 0.064
Montreal location L4	0.83 (0.43-1.59)	0.57		
Montreal behaviour (reference B3) B1 B2	 0.54 (0.23-1.31) 0.46 (0.20-1.07)	 0.17 0.07	 Removed	 0.49 0.25
EIM	2.08 (1.07-4.07)	0.03	Removed	0.11
Weight (kg)	1.00 (0.98-1.02)	0.87		
Current smoker	0.93 (0.63-1.36)	0.69		
Family history of IBD	0.97 (0.53-1.93)	0.97		
Prior bowel resection	0.91 (0.53-1.56)	0.73		
Prior perianal surgery	0.47 (0.24-0.91)	0.25	Removed	0.99
Exposure to anti-TNF	0.79 (0.44-1.42)	0.44		
Steroids at induction	0.76 (0.43-1.33)	0.33		
5-ASA at induction	0.50 (0.24-1.03)	0.06	Removed	0.15
CIM induction (reference no CIM) Sub therapeutic TGN Therapeutic TGN	 0.71 (0.24-2.05) 1.58 (0.83-3.02)	 0.52 0.17		
Semester CIM (reference no CIM) Sub therapeutic TGN Therapeutic TGN	 0.94 (0.34-2.58) 3.91 (2.04-7.53)	 0.90 <0.0001	 1.11 (0.37-3.26) 3.71 (1.87-7.34)	 0.86 <0.0001
CRP at induction	0.56 (0.97-1.01)	0.56		
Albumin at induction	1.01 (0.86-1.06)	0.81		

ADA = adalimumab, EIM = extra-intestinal manifestation, IBD = inflammatory bowel disease, CIM = concomitant immunomodulation, TGN = thioguanine nucleotide, CRP = c-reactive protein, HBI = Harvey-Bradshaw Index

Table 4.4 Univariate and multivariate predictors of ADA failure

Covariant	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Gender (reference female)	0.42 (0.19-0.93)	0.03	0.39 (0.17-0.91)	0.028
Age at diagnosis	0.99 (0.96-1.04)	0.94		
Disease duration at start of ADA	1.01 (0.97-1.06)	0.60		
Montreal location (reference L3)				
L1	1.74 (0.63-4.80)	0.28		
L2	1.34 (0.55-3.26)	0.51		
Montreal location L4	0.82 (0.45-2.75)	0.82		
Montreal behavior (reference B3)				
B1	0.49 (0.17-1.39)	0.18		
B2	0.84 (0.34-2.09)	0.71		
Perianal disease	1.15 (0.54-2.47)	0.72		
EIM	0.40 (0.12-1.32)	0.13		
Weight (kg)	0.98 (0.95-1.01)	0.18		
Current smoker	1.07 (0.64-1.78)	0.80		
Family history of IBD	0.32 (0.52-2.02)	0.23		
Prior bowel resection	0.73 (0.34-1.55)	0.41		
Prior perianal surgery	1.10 (0.42-2.89)	0.85		
Exposure to anti-TNF	1.19 (0.54-2.60)	0.67		
Steroids at induction	1.61 (0.76-3.42)	0.21		
5-ASA at induction	1.81 (0.73-4.48)	0.20		
CIM induction (reference no CIM)				
Sub-therapeutic TGN	0.31 (0.04-2.38)	0.52	0.42 (0.04-2.38)	0.263
Therapeutic TGN	0.38 (0.16-0.91)	0.03	0.37 (0.15-0.89)	0.026
CRP at induction	1.01 (0.99-1.02)	0.37		
Albumin at induction	0.98 (0.92-1.03)	0.40		
HBI at induction	1.00 (0.91-1.10)	0.99		
ADA dose escalation	0.46 (0.19-1.11)	0.08	Removed	0.203

ADA = adalimumab, EIM = extra-intestinal manifestation, IBD = inflammatory bowel disease, CIM = concomitant immunomodulation, TGN = thioguanine nucleotide, CRP = c-reactive protein, HBI = Harvey-Bradshaw Index

Supplement Table 4.1 – (A) CRP and HBI based on response status at week 12. (B) CRP and HBI normalization based on response at week 12

(A)

Response (n)	Pretreatment CRP (mg/L) Mean (median)	Week 12 CRP (mg/L) Mean (median)	Pretreatment HBI Mean (median)	Week 12 HBI Mean (median)
No response	31.97 (18.00)	32.66 (12.00)	8.68 (8)	9.32 (8)
Partial response	20.00 (8.00)	9.81 (5.00)	7.13 (8)	4.63 (4)
Complete response	18.77 (10.00)	4.35 (2.50)	7.49 (8)	1.61 (1)

(B)

	No response	Partial response	Complete response	p
HBI ≤ 4 n (%)	2 (10)	4 (50)	75 (92)	P<0.0001
CRP (<5mg/L) n (%)	7 (30)	5 (63)	75 (84)	P<0.0001
CRP (<5mg/L) & HBI ≤ 4 n(%)	1 (4.8)	2 (25)	62 (76.5)	P<0.0001

Supplement table 4.2: Univariate and multivariate predictors of ADA dose escalation

Covariant	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Gender (reference female)	1.18 (0.60-2.33)	0.63		
Age at diagnosis	1.01 (0.98-1.05)	0.57		
Disease duration at start of ADA	0.98 (0.94-1.02)	0.38		
Montreal location (reference L3) L1 L2	 1.41 (0.52-3.81) 1.64 (0.74-3.62)	 0.50 0.22		
Montreal location L4	0.84 (0.35-2.04)	0.70		
Montreal behavior (reference B3) B1 B2	 1.20 (0.46-3.14) 0.97 (0.37-2.53)	 0.71 0.94		
Perianal disease	1.04 (0.50-2.15)	0.92		
EIM	0.95 (0.43-2.12)	0.91		
Weight (kg)	0.99 (0.97-1.02)	0.89		
Weight at dose escalation (Kg)	1.01 (0.98-1.03)	0.64		
Current smoker	0.95 (0.58-1.57)	0.85		
Family history of IBD	1.31 (0.59-2.87)	0.51		
Prior bowel resection	0.84 (0.43-1.66)	0.62		
Prior perianal surgery	1.07 (0.44-2.63)	0.88		
Exposure to anti-TNF	1.37 (0.68-2.78)	0.38		
Steroids at induction	1.72 (0.86-3.45)	0.12		
5-ASA at induction	2.54 (1.15-5.65)	0.02	3.98 (1.68-9.40)	0.002
CIM induction (reference no CIM) Sub-therapeutic TGN Therapeutic TGN	 0.23 (0.03-1.71) 0.51 (0.23-1.09)	 0.15 0.08	Removed	0.30
CRP at induction	1.01 (1.00-1.02)	0.03	1.01(1.001-1.02)	0.035
Albumin at induction	0.98 (0.93-1.03)	0.33		
HBI at induction	1.05 (0.98-1.12)	0.20		
ADA dose escalation	0.46 (0.19-1.11)	0.08		

Figure 4.1 Flow diagram of patient recruitment. ADA = adalimumab

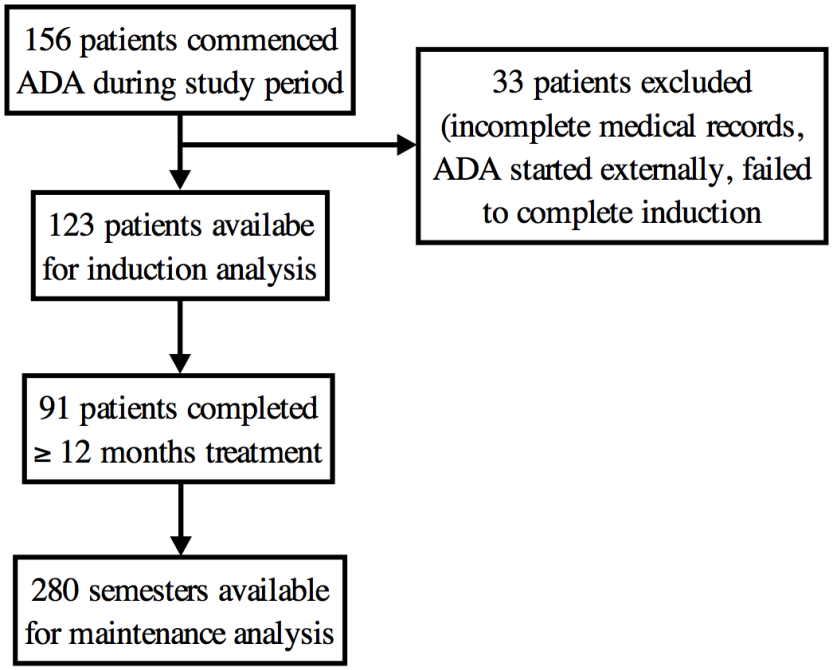

Figure 1. Patient recruitment. ADA = adalimumab

Figure 4.2 Clinical response after induction comparing concomitant immunomodulation to adalimumab monotherapy. Complete response to induction was observed more frequently in patients treated with ADA and CIM compared to ADA monotherapy (83.1 vs 60.9%, p = 0.02) CIM = concomitant immunomodulation, ADA = adalimumab

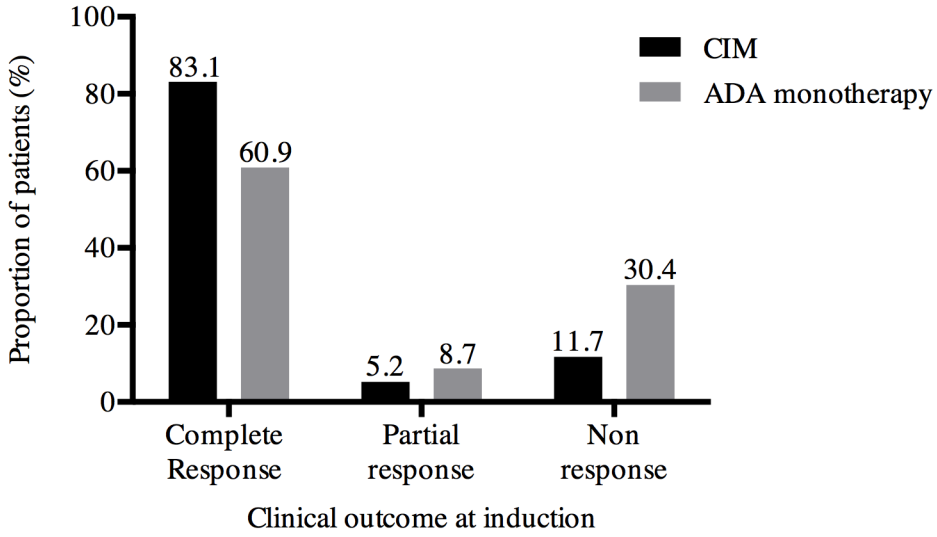

Figure 2. Clinical response after induction of concomitant immunomodulation vs. adalimumab monotherapy.
Complete response to induction was observed more frequently in patients treated with CIM compared to ADA monotherapy (83.1 vs 60.9%, p = 0.02)
CIM = concomitant immunomodulation, ADA = adalimumab

Figure 4.3 **Clinical response after induction stratified by TGN and ADA monotherapy.** Complete response was observed more frequently in patients with therapeutic TGN vs sub-therapeutic TGN vs ADA monotherapy (87.3 vs 70.0 vs 60.9%, p = 0.011). TGN = thioguanine nucleotide, ADA = adalimumab monotherapy

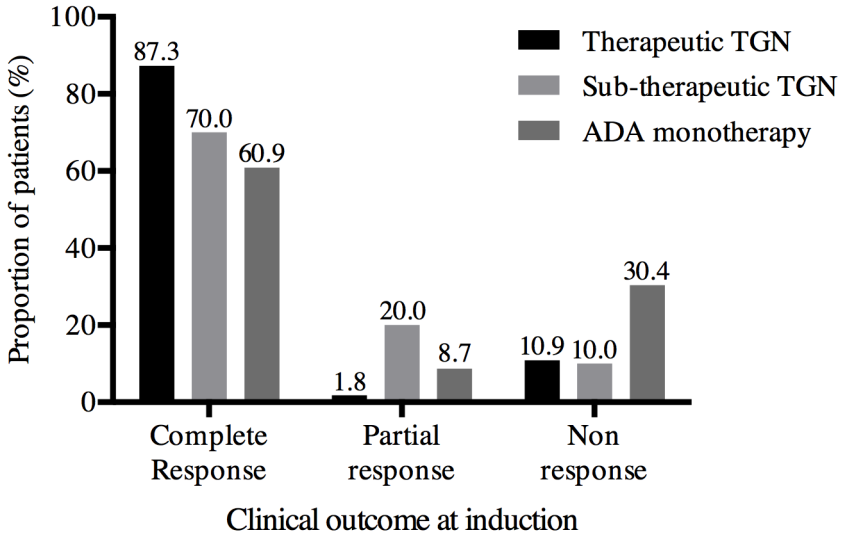

Figure 3. Clinical response after induction stratified by TGN and ADA monotherapy
Complete response was observed more frequently in patients with therapeutic TGN vs sub-therapeutic TGN vs ADA monotherapy (87.3 vs 70.0 vs 60.9%, p = 0.011)
TGN = thioguanine nucleotide, ADA = adalimumab monotherapy

Figure 4.4 Association between semester outcomes overall, and according to CIM and TGN status.

CIM = concomitant immunomodulation, TGN = thioguanine nucleotide level

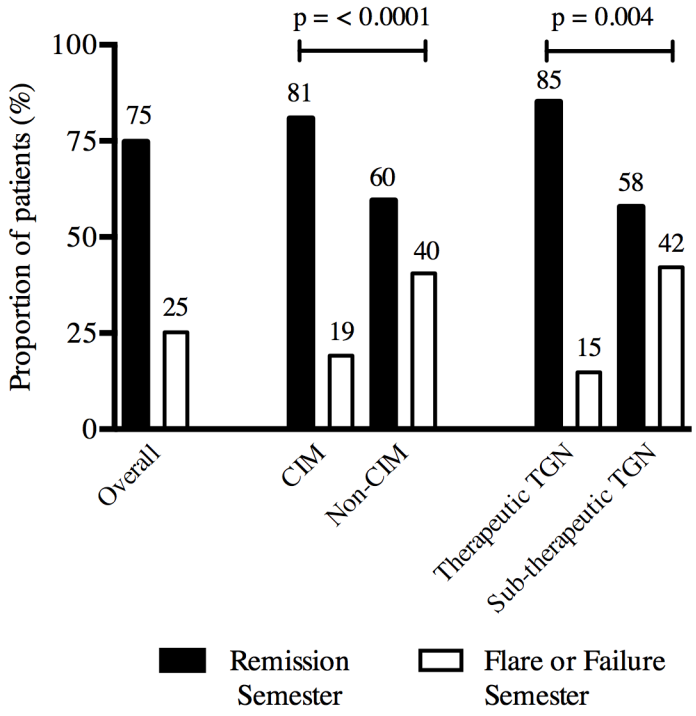

Figure 4. Association between semester outcomes overall and according to CIM and TGN status. CIM = concomitant immunomodulation, TGN = thioguanine nucleotide level

Figure 4.5 **Time to adalimumab failure.** Kaplan-Meier analysis illustrating time to ADA failure (months) in patients treated (n = 77) and not treated (n = 46) with CIM for ≥3 months prior to commencing ADA (and continued for first 6 months). CIM = concomitant immunomodulation, ADA = adalimumab

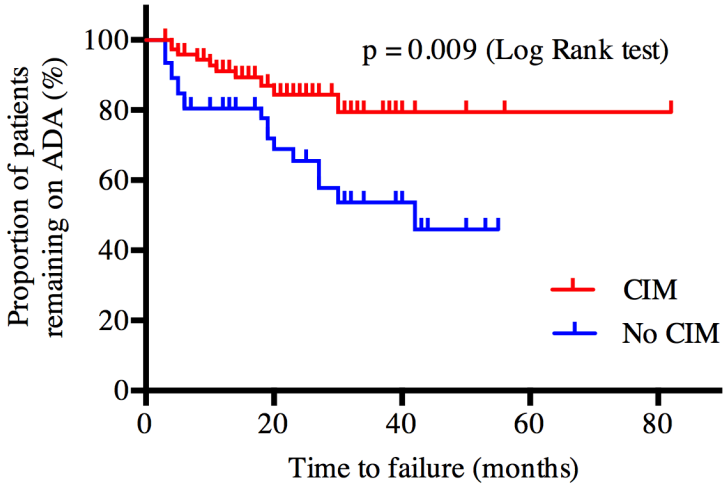

Figure 5. Time to adalimumab failure. Kaplan-Meier analysis illustrating time to ADA failure (months) in patients treated (n = 77) and not treated (n = 46) with CIM for ≥ 3 months prior to commencing ADA (and continued for first 6 months). CIM = concomitant immunomodulation, ADA = adalimumab

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CHAPTER 5 (STUDY 4) USE AND OF IMMUNOMODULATORS IN ELDERLY IBD PATIENTS AND ITS IMPACT ON SURGICAL OUTCOMES

This chapter is presented as a published journal article, “Comorbidities Rather Than Age Are Associated with the Use of Immunomodulators in Elderly-onset Inflammatory Bowel Disease” in manuscript format.

Comorbidities Rather than Age are Associated with the Use of Immunomodulators in Elderly Onset Inflammatory Bowel Disease

Short title – Immunomodulators use in the elderly

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Non-Standard abbreviations:

AZA – Azathioprine; CCI - Charlson comorbidity index; IMS – Immunomodulators; 6-MP – Mercaptopurine; MTX – Methotrexate

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Contribution: VK contributed to study design, data acquisition, analysis, and wrote and revised the manuscript. SK and FM contributed to analysis and writing up of the manuscript. CS, PK, BJ, CM, GB, GC, JC, PL, KM, RW, TH, JA and PP contributed to data acquisition and manuscript revision. RL contributed to study design, manuscript revision and intellectual content.

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ALL authors approved the final version of the article, including the authorship list.

5.1 Abstract

Background and aims

The use of immunomodulators (IMs) is often avoided in elderly patients with inflammatory bowel disease (IBD) due to concerns about complications. Our aim is to compare the use of IMs in elderly and younger patients with Crohn's disease (CD) or ulcerative colitis (UC) and identify markers that predict their use.

Methods

In this retrospective cohort study, patients diagnosed with IBD from 1970 to 2009 were recruited from the "Sydney IBD Cohort". Patients diagnosed at age ≥60 and between 16-40 were classified as 'elderly-onset' and 'young-onset' respectively.

Results

Total of 255 elderly-onset patients (115 CD, 140 UC) and 1244 young-onset patients (657 CD, 587 UC) were recruited. Most elderly-onset patients had colonic CD (61.4%), whereas young-onset patients had predominantly ileocolonic CD (42.8%, P<0.0001). Left-sided UC was the most common disease localisation for both elderly-onset (52.1%) and young-onset patients (42.2%, P=0.013). The cumulative probability of IM exposure at 5 years post diagnosis was significantly less in elderly-onset patients compared to young-onset patients for CD (20.0% vs 33.4%, P=0.0002) and UC (7.8% vs 13.4%, P=0.0007). Age at diagnosis was not associated with the time to IMs introduction. Charlson Comorbidity Index was shown to delay IM introduction in CD (HR 0.863, 95%CI 0.787-0.946, P=0.002) and UC (HR 0.807, 95%CI 0.711-0.917, P=0.001). Early IM use was associated with reduced need for abdominal and perianal surgery in CD (HR 0.177, 95% CI 0.089-0.351, P<0.0001).

CONCLUSIONS

Comorbidity and not age at diagnosis is associated with IM introduction. Early IM is associated with reduced surgery in both young and elderly onset CD but not UC

Keywords: inflammatory bowel disease; geriatric; elderly; ageing; immunomodulators; surgery

5.2 INTRODUCTION

Inflammatory bowel disease (IBD) comprising Crohn's disease (CD) and ulcerative colitis (UC), are inflammatory disorders that typically affect the younger age group. Patients aged 60 or older comprise only 10-15% of incident IBD cases[1,2]. Currently, there are no age-specific treatment guidelines for elderly-onset IBD. Because the natural history of IBD varies according to the age of onset, the current management practices designed for adult patients may not be applicable to the elderly[3,4]. Presence of comorbidity and polypharmacy in elderly patients further underpins the challenges associated with managing this population[5] at risk of opportunistic infections and cancers

The conventional treatment practice adopts a "step-up" approach starting with 5-aminosalicylic acid (5-ASA). Thus, most studies are unable to demonstrate the positive effects of immunomodulators (IMs) due to their use in a more severe disease, after development of strictures or fistulas or insufficient patient-years of follow-up. Recent evidences demonstrate efficacy in the "top-down" approach which involves introducing IMs and biologics early in the disease course[6,7]. This may be more effective in controlling inflammation and preventing irreversible damage to the intestinal mucosa from the first flare-up than the "step-up" approach[8,9]. Additionally, introduction of IMs early in the disease course has been suggested to delay first major surgery for CD[6,10].

IMs are used to maintain remission in steroid-dependent or refractory patients[11]. Their use in the elderly is tentative due to higher risks of adverse effects and opportunistic infections[12,13]. IMs can cause adverse events in approximately 15% of patients and this can be classified into allergic (pancreatitis, fever, rash and arthralgia) and non-allergic (leukopenia, thrombocytopenia, infection and hepatitis) reactions. Of a greater concern is the increased risk of malignancy as patients aged

≥65 receiving thiopurines were found to be 2.6 times more likely to develop lymphoma than their younger counterparts[14]. Physicians may therefore avoid IMs use in older patients with IBD.

Data on surgical outcome within the elderly-onset IBD patients are scarce. Elderly CD patients undergo surgery less often compared to their younger counterparts, whereas the rates are comparable for elderly UC and adult UC patients[15]. It is unclear whether elderly onset CD takes a generally milder course or whether physicians have higher threshold for surgical interventions. Elderly patients with IBD experience higher rate of postoperative morbidity and mortality, as well as increased length of hospital stay and operation time[16,17]. Given the preventative effects of IMs on surgery, elderly patients with IBD may benefit from early treatment if those likely to require the therapy could be identified at diagnosis.

We hypothesized that elderly onset patients with IBD were less likely to receive IMs for IBD and that the decision to avoid IMs is driven by age. The primary study aim therefore was to compare IMs prescription rates between elderly onset and younger IBD patients with a view to identifying patients characteristics and clinical markers at presentation that predict the initiation of IMs therapy. The secondary outcome was the impact of early IMs use on the requirement of first surgery due to IBD.

5.3 Materials and methods

Population

Data of ambulatory patients with IBD from 1942 to 2014 were retrospectively collected from 2 tertiary hospitals and 6 private consultant rooms in Sydney metropolitan region. The “Sydney IBD

cohort" was first described in 1994 and the methodology was repeated in 2010 and 2012 to augment the cohort[18]. Diagnoses were confirmed retrospectively by a review of the clinical and endoscopic reports as well as radiological, histological and pathological investigations. To focus on a more recent cohort of patients and with adequate duration of follow up, only those with a definitive diagnosis of CD or UC between January 1, 1970 and December 31, 2009 were included. Patients with indeterminate colitis or those who had a change of diagnosis to a non-IBD pathology were excluded.

Patients were categorised into 2 groups according to their age at diagnosis. The first group of patients who were diagnosed at age 60 or older were classified as 'elderly-onset' IBD patients. The second group consisted of patients diagnosed from 16 to 40 years of age and were referred as 'young-onset' IBD patients.

DATA COLLECTION

All demographic data in addition to medical therapy and surgical interventions were collected. Clinical records, operation reports and discharge summaries were reviewed for patient demographics, disease characteristics, use of medications, surgical history, and presence of polypharmacy and comorbidity. Those lost to follow-up were contacted, and if unavailable, were excluded as of their last observation. Disease characteristics were categorised at diagnosis according to the Montreal classification and any changes with the treatment were updated until the most recent follow-up.

Medical therapy consisted of 5-ASA, corticosteroid, IMs (Azathioprine (AZA), Mercaptopurine (6-MP) and methotrexate (MTX)) and anti-tumour necrosis factor (TNF) alpha agents (adalimumab and infliximab). Long-term steroid use was referred as ≥6 months of continuous use of steroids within a 12-month period. Those who used either AZA, 6-MP or MTX continuously for 6 months were considered as being "maintained" by IMs. Early IM use was defined as introduction of an IM within 3 years of diagnosis and being on the medication continuously for ≥6 months[6].

Patients' comorbid status was quantitatively expressed using the Charlson comorbidity index (CCI)[19] at the time of diagnosis. Rate of hospitalisation was calculated by dividing the total number of IBD-related hospital admissions by the duration of follow-up. Details of major abdominal, perianal or resectional surgeries were recorded. Simple surgical interventions under anaesthesia without abscess drainage were excluded.

TREATMENT PRACTICES

Throughout the study period, thiopurines were used as the first IM of choice, with AZA used more preferentially than 6-MP. Typical dosing of AZA was 2 to 2.5mg/kg body weight, and for 6-MP it was 1 to 1.5mg/kg body weight. Consistent with the national guidelines, MTX replaced AZA/6-MP when a patient became intolerant to the drug. Patients with thiopurine methyltransferase deficiency or arthritic extraintestinal manifestation were initiated on MTX immediately. MTX was prescribed at an initial dose of 25mg per week with maintenance dosing of 15mg per week thereafter, taken either orally or parenterally. IM therapy was ceased in cases of failure, adverse events, patient non-compliance, pregnancy, and/or other patient circumstances. Otherwise, once initiated, IMs were prescribed continuously.

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS software version 23.0. Qualitative data was reported as percentages and was analysed using chi-square test. Continuous variables were described using either median and interquartile range (IQR) and analysed with the Mann-Whitney U test if non-parametrically distributed. Normally-distributed continuous variables were described using mean and standard deviation and analysed using the T test. A P-value of <0.05 was considered statistically significant.

Survival analyses of the IM introduction and surgery were calculated using the log-rank score and were displayed on the Kaplan-Meier curve. Hazard ratios (HR) were calculated using Cox proportional hazards regression models (both univariate and multivariate) with 95% confidence intervals (CI) when determining predictors of IM exposure and surgery. All baseline characteristics at diagnosis, medication use, comorbidity and polypharmacy were tested using the univariate analysis. Any variables with P-value less than 0.1 were included into the multivariate analysis.

Ethical consideration

Ethics approval was obtained from the Sydney Local Health District Human Research Ethics Committee (HREC/10/CRGH/126).

5.4 Results

Patient demographics

A total of 255 elderly-onset (115 CD, 140 UC) patients and 1,244 young-onset (657 CD, 587 UC) patients were recruited (Table 5.1). The median duration of follow-up was 8.0 (IQR 3.0-13.0) for the elderly-onset group and 11.0 (IQR 5.0-20.0) for the young-onset group for CD (P<0.0001). For UC, the median duration of follow-up was 8.0 (IQR 3.0-14.8) for the elderly-onset group and 11.0 (IQR 4.0-20.0) for the young-onset group (P<0.0001).

The ileocolonic CD phenotype was the commonest location in young-onset patients (42.8%), whereas colonic CD was found in 61.4% of elderly-onset patients (P<0.0001). In UC, left-sided location was the commonest location for both young-onset (42.2%) and elderly-onset groups (52.1%, P=0.013).

MEDICAL INTERVENTIONS

A significantly lower proportion of elderly-onset CD patients compared to young-onset CD patients were exposed to (24.5% vs 49.7%, P<0.0001) and maintained on (19.0% vs 42.5%, P<0.0001) IMs (Table 5.2). In UC, IM exposure (8.1% vs 20.5%, P=0.001) and IM maintenance (5.2% vs 16.5%, P=0.001) were considerably lower in elderly-onset versus young-onset groups respectively (Table 5.2). In UC, early IM use was significantly lower in the elderly-onset (3.0%) versus the young-onset group (7.8%, P=0.048). Thiopurine was the commonest IM prescribed to both elderly-onset and young-onset groups in CD and UC.

In CD, the cumulative probability of IM exposure at 5 years after diagnosis was 20.0% in elderly-onset patients versus 33.4% in young-onset patients (P=0.002, Figure 5.1a). In UC, the cumulative probability of IM exposure at 5 years after diagnosis was 7.8% in elderly-onset patients and 13.4% in young-onset patients (P=0.007, Figure 1b).

COMORBIDITY, POLYPHARMACY AND RATE OF HOSPITALISATION

Elderly-onset subjects had significantly higher comorbidities than young-onset subjects in both CD (median CCI: 5.0 [IQR: 2.0-6.0] versus median CCI: 0.0 [IQR: 0.0-1.0] respectively, P<0.0001) and in UC (median CCI: 5.0 [IQR: 4.0-7.0] versus median CCI: 1.0 [IQR: 0.0-2.0] respectively, P<0.0001). Pearson's correlation analysis was performed between age and CCI. Correlation was 0.58 (p<0.0001) in the CD cohort and 0.79 (p<0.0001) in the UC cohort.

The median total number of medications taken was 8.0 (IQR 4.75-9.25) by elderly-onset CD compared to 2.0 (IQR 1.0-3.0) for young-onset CD. For UC, the median was 6.0 (IQR 3.0-9.0) for elderly-onset and 2.0 (IQR 1.0-3.0) and young-onset groups (P<0.0001). Elderly-onset patients were admitted to hospital more frequently than young-onset patients for both CD and UC. In CD,

there were 0.23±0.40 hospital admissions per year in young-onset patients and 0.41±0.82 hospital admissions per year in elderly-onset patients (P=0.023). Young-onset UC patients were admitted 0.09 ± 0.26 times per year, while elderly-onset UC patients were admitted 0.23 ± 0.54 times per year (P<0.0001).

FACTORS AFFECTING TIME TO INITIATION OF IM THERAPY

For both UC and CD, age of diagnosis was not associated with the time at which IMs were introduced (Tables 5.3). In CD, CCI was significantly associated with delayed introduction of IM (HR: 0.86, 95%CI: 0.79-0.95, *P*=0.002). Out of the baseline characteristics considered, only extra-intestinal manifestation was associated with early introduction of IM (HR: 1.47, 95%CI: 1.01-2.14, *P*=0.042). Long-term steroid use (HR: 1.91, 95%CI: 1.42-2.58, *P*<0.0001), anti-TNF use (HR: 1.68, 95%CI: 1.20-2.34, *P*=0.003) and number of hospital admissions per year (HR: 1.49, 95%CI 1.22-1.81, *P*<0.0001) were associated with the need for earlier IM therapy.

In UC, multivariate analysis revealed that having higher CCI predicted for delayed use of IM (HR: 0.81, 95%CI: 0.71-0.92, *P*=0.001). Proctitis (HR: 0.45, 95%CI: 0.23-0.89, *P*=0.021) was associated with delayed initiation of IMs compared to pancolitis. Long-term steroid use (HR: 4.45, 95%CI 2.69-7.36, *P*<0.0001), anti-TNF exposure (HR: 2.12, 95%CI: 1.03-4.40, *P*=0.042) and number of hospital admissions per year (HR: 2.21, 95%CI: 1.24-3.94, *P*=0.007) were associated with the need for earlier IM therapy.

FACTORS AFFECTING TIME TO FIRST IBD-RELATED SURGERY

The 10-year cumulative probability of undergoing major abdominal or perianal surgery for CD was 27.0% for elderly-onset patients versus 42.7% for young-onset patients (*P*=0.003, Figure 5.2a).

Median time to first surgery was 5.0 years (IQR: 2.0-11.2) for young-onset patients and 5.5 years (IQR: 2.0-10.0) for elderly-onset patients (*P*=0.477). Multivariate analysis revealed that early IM use was associated with delayed need for surgery (HR: 0.18, 95%CI: 0.09-0.35, *P*<0.0001, Table 5.4). Patients with colonic CD (HR: 0.25, 95%CI: 0.13-0.48, *P*<0.0001) were less likely to require surgery than ileocolonic CD. Patients with the inflammatory phenotype (HR: 0.44, 95%CI: 0.26-0.74, *P*=0.002) were less likely to have early surgery than those with the penetrating phenotype. Frequent hospitalisation was also an indicator for earlier surgery (HR 1.48, 95%CI: 1.23-1.77, *P*<0.0001).

For UC, the 10-year cumulative probability of undergoing colectomy was 10.9% for elderly-onset patients and 5.9% for young-onset patients (*P*=0.22, Figure 5.2b). Median time to first intestinal resection was 7.0 years (IQR: 3.0-13.0) for elderly-onset patients versus 11.0 years (IQR: 4.0-20.0) for young-onset patients (*P*<0.0001). On multivariate analysis, proctitis (HR: 0.18, 95%CI: 0.07-0.48, *P*=0.001) and left-sided UC (HR: 0.29, 95%CI: 0.16-0.54, *P*<0.0001) were less likely to require a surgery than pancolitis (Table 5.4). Long-term steroid use (HR: 3.45, 95%CI: 1.85-6.43, *P*<0.0001), anti-TNF use (HR: 8.17, 95%CI: 2.74-24.42, *P*<0.0001) and the number of hospital admissions per year (HR: 3.05, 95%CI: 1.95-4.76, *P*<0.0001) were predictors for early surgery. Early IM use was not a significant predictor of colectomy on the univariate model.

5.5 Discussion

In this cohort study, we examined the factors driving the use of IMs for IBD in eldery-onset versus young-onset patients with IBD. In contrast to our hypothesis, age-related factors including comorbid status rather than age itself were associated with IMs use. Comorbidity was shown to delay the time at which IMs were introduced in both CD and UC whereas age at diagnosis was not associated with IMs introduction. Physicians, therefore, did not base IMs treatment on age alone.

Comorbidities influenced the use of IMs and the overall use of IMs, therefore, was significantly lower in elderly-onset IBD patients than in young-onset IBD patients.

The decrease rate in IMs prescription in the elderly is consistent with many studies.[15,20-22] It is often hypothesised that this difference in utilisation may have been due to lower disease severity in the elderly, particularly for CD.[23] In contrast to other studies, we found that elderly onset patients may also experience severe disease: the rates of hospitalisations for examples were higher for elderly onset IBD patients than those with young onset. The requirement for surgery was greater for elderly onset patients with UC, and although less elderly onset patients with CD required surgery, the time to surgery was similar to young onset patient. Based on our data it is therefore questionable whether elderly onset IBD is per se prone to take a milder course.

Elderly patients experience complications associated with IMs more frequently than younger patients, contributing to their lesser use.[14,24,25] Although steroid dependence has been shown to be more common in the elderly,[26] this was not seen in our cohort in which long term steroid usage was similar between the two age-groups. Steroid sparing IMs, therefore, might be advantageous in the elderly IBD patients despite the potential for side effects [14,27, 28] which are more common in the elderly. These side effects should be put in the balance when prescribing these drugs to the elderly who on the other hand are frail and less able to tolerate severe or prolonged periods of disease activity. [29] Our study showed no difference between the two groups in the proportion of patients who stopped the IM after being initiated. Although the exact reasons are not available, we assume that side effects constitute an important cause for discontinuing the drug.

Comorbidity is an exemplary age-related factor that is more prevalent in the elderly than in younger populations. Most studies on elderly-onset IBD fail to acknowledge the importance of comorbidity when assessing patients' treatment outcome. Whilst this study confirms the lesser use of IMs within the elderly, age of diagnosis itself was not a factor that restricted the use of IMs.

Instead, it is comorbidity that delayed the initiation of IM therapy. Comorbidity can alter the prognosis of IBD and increase the likelihood of drug-to-drug interaction[5]. Thus, it appears that physicians base their decision in elderly onset patients appropriately on comorbidity rather than age.

Fewer elderly-onset CD patients underwent surgery compared to young-onset CD patients. In UC, the opposite was observed until 20 years after diagnosis, which then the probability converged for the two groups. Two factors may contribute to this observation. First, given that more elderly-onset patients presented with left-sided or pancolitic UC, elderly-onset UC may progress as a more aggressive disease than young-onset UC. Pancolitis being associated with increased risk of colectomy, may also support this finding. Secondly, surgical risk is highest among patients with ileal or ileocolonic disease[6]. Thus, without being curative, surgery in the elderly CD is less imperative and potentially harmful, due to higher risk of postoperative complications and longer hospital stay[16,17]. Surgery for UC, however, is curative, thus physicians and patients may prefer a more definite surgical intervention than long term IM therapy. Likewise, a Pennsylvanian study by Juneja et al[15] found that patients with CD diagnosed at <65 years of age were more likely to undergo surgery than those diagnosed at ≥65 years of age. However, the UC colectomy rate in this cohort was similar among the two groups.

The recommended clinical practice is evolving towards the "top-down" approach with early initiation of immunosuppressive therapy. Such therapy ensures patients' quality of life throughout the disease course and be more efficacious in inducing remission than the conventional approach[7]. We observed that early IM use (≤3 years since diagnosis) is associated with a delay in major abdominal or perianal surgery for CD. This was seen even among elderly onset patients, despite having a lower surgical rate and lower use. This observation has also been made by other studies[6,7,30]. This indicates that healthy elderly-onset patients with minimal comorbidities should be considered for early IM therapy to prevent future surgical risk. Similar finding was not displayed for UC, possibly due to smaller number of patients receiving IM.

The strengths of this study include its abundant patient-years of follow-up, and complete record of disease characterisation at diagnosis. The present study followed the standardised management regimes and case definitions that may be lacking in studies derived from insurance data, hospital coding, or de-identified data. The Montreal Classification system, which is an objective marker of disease severity, was employed to prevent bias associated with recall or misclassification. Such strategies were adopted in other Australian and New Zealand population-based studies. Most importantly, this was one of the few studies that identified age and age-related factors as separate variables when determining predictors of time to IM introduction.

There are a few limitations to this study. It is a retrospective study based on ambulatory specialist--referred cohort within the Sydney Local Health District. This mode of data acquisition and geographic isolation may have exposed the study to selection bias. However, recruitment of patients managed by gastroenterologists with exceptional longitudinal follow-up and documentation allowed precise characterisation of every cause and ensured the definition of IM was met. Secondly, our data was affected by changes in treatment practices and governmental regulations over the past decades. This may account for the smaller number of patients receiving biologics within the population.

In conclusion, young-onset IBD and elderly-onset IBD showed a distinct difference in disease phenotypes and medication use. Our study showed that in clinical practice age does not have a correlation with the time at which IMs are introduced but age-related factors, especially comorbidities, are used instead to assess the appropriateness of IMs therapy. Further research into the effects of comorbidity on efficacy and safety of IMs is required. Furthermore, newer agents such as gut directed therapy with Vedolizumab and potentially less side effects may prove a safer option for elderly onset patients in future. Meanwhile, IMs should be prescribed with care in patients with high comorbid status, regardless of their age or severity of disease. Elderly patients who are fit and healthy should be considered for earlier use of IMs in their disease course for maximal quality of life and to reduce risk of surgery.

Table 5.1 Demographics and Clinical Characteristics of Crohn's Disease and Ulcerative Colitis Patients at Diagnosis

	Crohn's Disease			Ulcerative Colitis		
	Young-onset (16-40)	Elderly-onset (≥60)	P	Young-onset (16-40)	Elderly-onset (≥60)	P
No. of patients	657	115		587	140	
Median age (IQR)	26 (22-31.5)	68 (64-76)	<0.0001	28 (24-33)	67 (64-74)	<0.0001
Median follow-up (IQR)	11 (5-20)	8 (3-13)	<0.0001	11 (4-20)	8 (3-14.8)	<0.0001
Patient-years of follow-up	8589	1002		7824	1327	
Gender, N (%)			0.295			0.048
Male	280 (42.6)	43 (37.4)		285 (48.6)	81 (57.9)	
Female	377 (57.4)	72 (62.6)		302 (51.4)	59 (42.1)	
Disease location, N (%)			<0.0001			
Ileal (L1)	161 (24.8)	15 (13.2)				
Colonic (L2)	211 (32.5)	70 (61.4)				
Ileocolonic (L3)	278 (42.8)	29 (25.4)				
Not documented	7	1				
Upper GI (L4), N (%)			0.181			
Yes	10 (1.5)	0 (0.0)				
No	637 (98.5)	114 (100)				
Not documented	10	1				
Disease phenotype, N (%)			0.947			
Inflammatory (B1)	427 (66.5)	78 (67.8)				
Stricturing (B2)	144 (22.4)	26 (22.6)				
Penetrating (B3)	70 (10.9)	11 (9.6)				
Not documented	15	0				
Perianal disease, N (%)			0.265			
Yes	126 (19.3)	17 (14.9)				
No	526 (80.7)	97 (85.1)				
Not documented	5	1				
Disease location, N (%)						0.013
Proctitis (E1)				201 (34.2)	30 (21.4)	
Left-sided (E2)				248 (42.2)	73 (52.1)	
Pancolitis (E3)				138 (23.5)	37 (26.4)	
Not documented				0	0	
Extra-intestinal, N (%)			0.787			0.509
Yes	117 (18.9)	22 (20.0)		90 (15.6)	18 (13.3)	
No	502 (81.1)	88 (80.0)		487 (84.4)	117 (86.7)	
Not documented	38	5		10	5	

Table 5.2 Medication Use in Crohn's Disease and Ulcerative Colitis Patients During Follow-up

	Crohn's Disease			Ulcerative Colitis		
	Young-onset (16-40) n=657	Elderly-onset (≥60) n=115	P	Young-onset (18-40) n=587	Elderly-onset (≥60) n=140	P
5-ASA (%)	538 (86.9)	94 (87.0)	0.972	559 (96.9)	139 (99.3)	0.112
Long-term steroids (%)	384 (60.8)	63 (57.3)	0.490	218 (37.1)	45 (32.1)	0.361
Anti-TNF (%)	66 (10.6)	3 (2.7)	0.009	17 (2.9)	1 (0.7)	0.142
IMs exposure (%)	309 (49.7)	27 (24.5)	<0.0001	118 (20.5)	11 (8.1)	0.001
IMs maintenance (%)	251 (42.5)	20 (19.0)	<0.0001	95 (16.5)	7 (5.2)	0.001
Early IM use (%)	147 (24.9)	18 (17.1)	0.086	45 (7.8)	4 (3.0)	0.048
Exposed IM Type (%)			0.001			0.845
Thiopurine	268 (86.7)	21 (77.8)		117 (92.9)	11 (91.7)	
MTX	1 (0.3)	2 (7.4)		2 (1.6)	0 (0.0)	
Both	40 (12.9)	4 (14.8)		7 (5.6)	1 (8.3)	
Median time to starting IMs, yr (IQR)	6.0 (2.0-16.0)	6.0 (1.5-13.0)	0.220	9.0(3.0-20.0)	8.0 (3.0-15.0)	0.077

Table 5.3 Univariate and Multivariate Predictors of Time to Initiation of IM Therapy and Time to Surgery in Crohn's Disease Patients

	Time to Initiation of IM Therapy				Time to Surgery			
Covariant	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Gender	0.94 (0.75-1.18)	0.59			1.18 (0.93-1.50)	0.18		
Age groups	0.53 (0.35-0.80)	0.003		0.45	0.54 (0.35-0.82)	0.004		0.86
Disease location		0.55				<0.0001		<0.0001
Ileal (L1)	0.86 (0.64-1.15)	0.31			1.36 (1.05-1.77)	0.02	1.21 (0.82-1.78)	0.33
Colonic (L2)	0.90 (0.70-1.17)	0.45			0.29 (0.20-0.40)	<0.0001	0.25 (0.13-0.48)	<0.0001
Ileocolonic (L3)	Reference				Reference			
Disease phenotype		0.63				<0.0001		0.001
Inflammatory (B1)	0.84 (0.59-1.20)	0.34			0.29 (0.20-0.40)	<0.0001	0.44 (0.26-0.74)	0.002
Stricturing (B2)	0.88 (0.58-1.31)	0.52			0.90 (0.63-1.29)	0.57	0.89 (0.52-1.51)	0.66
Penetrating (B3)	Reference				Reference			
Perianal involvement	1.64 (1.27-2.12)	<0.0001		0.30	0.88 (0.64-1.21)	0.43		
Extra-intestinal	1.35 (1.02-1.78)	0.04	1.47 (1.01-2.14)	0.04	0.76 (0.55-1.06)	0.10		
5-ASA use	0.85 (0.61-1.18)	0.33			0.57 (0.41-0.79)	0.001		0.13
Long-term steroids use	1.45 (1.13-1.85)	0.003	1.91 (1.42-2.58)	<0.0001	1.58 (1.21-2.08)	0.001	1.70 (1.17-2.48)	0.006
Anti-TNF use	3.79 (2.88-4.99)	<0.0001	1.68 (1.20-2.34)	0.003	1.03 (0.69-1.53)	0.89		
Early IM use					0.23 (0.13-0.39)	<0.0001	0.18 (0.09-0.35)	<0.0001
CCI	0.87 (0.80-0.95)	0.002	0.86 (0.79-0.95)	0.002	0.23 (0.13-0.40)	<0.0001	0.18 (0.09-0.35)	<0.0001
Number of medications	1.01 (0.96-1.05)	0.83			1.08 (0.99-1.17)	0.07		
CD-related surgery	0.99 (0.79-1.24)	0.92			1.04 (0.98-1.10)	0.17		
Number of hospital admissions per year	1.53 (1.33-1.75)	<0.0001	1.49 (1.22-1.81)	<0.0001	1.58 (1.36-1.83)	<0.0001	1.48 (1.23-1.77)	<0.0001

Table 5.4 Univariate and Multivariate Predictors of Time to Initiation of IM Therapy and Time to Surgery in Ulcerative Colitis Patients

	Time to Initiation of IM Therapy				Time to Surgery			
Covariant	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Gender	0.74 (0.53-1.05)	0.096		0.67	0.72 (0.42-1.22)	0.22		
Age groups	0.44 (0.24-0.82)	0.010		0.12	1.49 (0.78-2.84)	0.22		
Disease location Proctitis (E1) Left-sided (E2) Pancolitis (E3)	 0.30 (0.17-0.54) 1.04 (0.71-1.53) Reference	<0.0001 <0.0001 0.83	0.45 (0.23-0.89)	0.066 0.021	 0.11 (0.04-0.28) 0.27 (0.15-0.49) Reference	<0.0001 <0.0001 <0.0001	 0.18 (0.07-0.48) 0.29 (0.16-0.54)	<0.0001 0.001 <0.0001
Extra-intestinal	1.32 (0.86-2.02)	0.20			1.26 (0.66-2.39)	0.48		
5-ASA use	20.94 (0.18-2495)	0.21			20.91 (0.01-32271)	0.42		
Long-term steroids use	4.90 (3.30-7.27)	<0.0001	4.45 (2.69-7.37)	<0.0001	4.40 (2.43-7.94)	<0.0001	3.45 (1.85-6.43)	<0.0001
Anti-TNF use	9.48 (5.65-15.92)	<0.0001	2.12 (1.03-4.40)	0.04	4.29 (1.70-10.80)	0.002	8.17 (2.74-24.42)	<0.0001
Early IM use					0.36 (0.05-2.59)	0.31		
CCI	0.78 (0.68-0.90)	0.001	0.81 (0.71-0.92)	0.001	0.36 (0.05-2.60)	0.31		
Number of medications	1.02 (0.97-1.08)	0.42			0.82 (0.56-1.20)	0.31		
UC-related surgery	1.25 (0.75-2.08)	0.40			0.98 (0.83-1.16)	0.83		
Number of hospital admissions per year	2.15 (1.66-2.79)	<0.0001	2.21 (1.24-3.95)	0.007	5.45 (3.58-8.29)	<0.0001	3.05 (1.95-4.76)	<0.0001

Figure 5.1 Cumulative probability of IM exposure over time since diagnosis in elderly-onset and young-onset patients with CD (1a, P=0.002) and UC (1b, P=0.007).

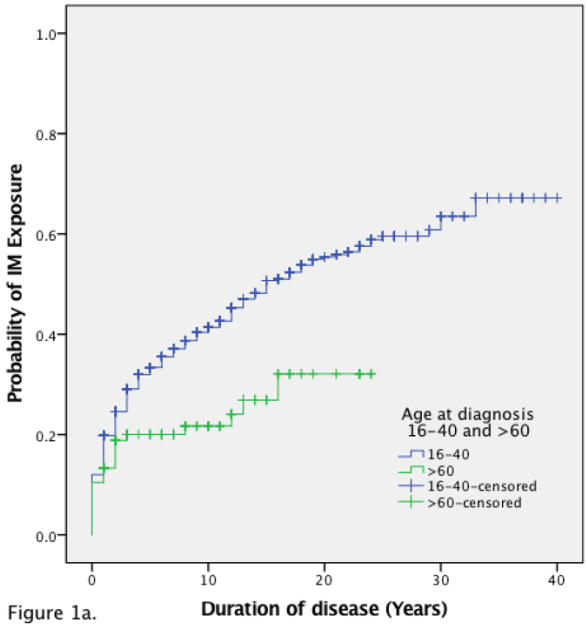

Figure 1a.

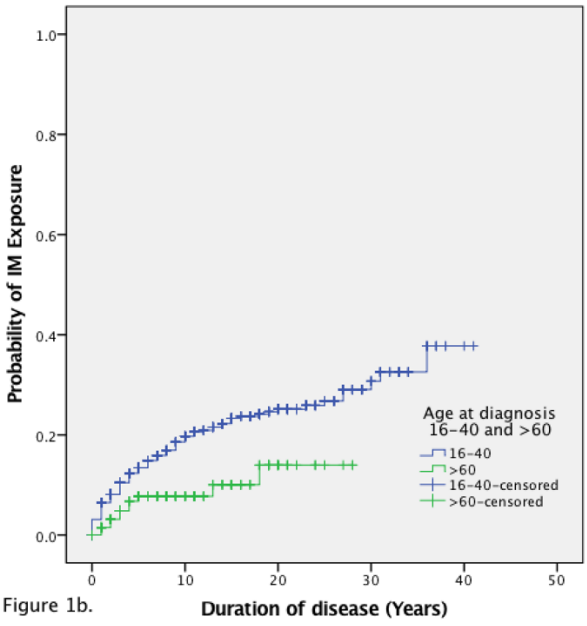

Figure 1b.

Figure 5.2Cumulative probability of first IBD-related surgery since diagnosis in elderly-onset and young-onset patients with CD (2a, P=0.003) and UC (2b, P=0.219).

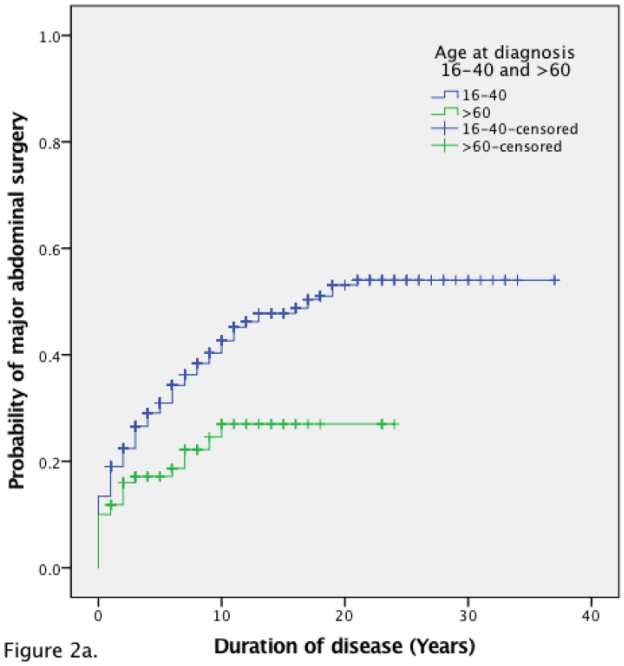

Figure 2a.

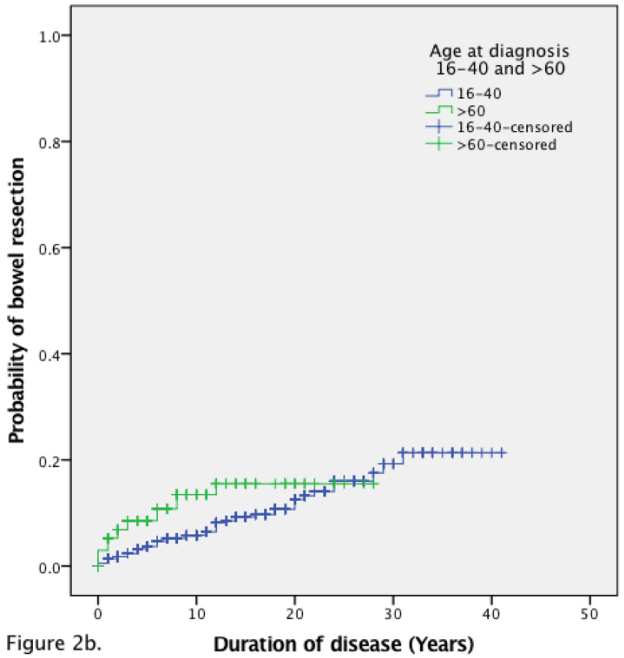

Figure 2b.

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CHAPTER 6 (STUDY5) GASTROENTEROLOGISTS' PREFERENCE ON THE USE OF IMMUNOMODULATORS AND BIOLOGICAL THERAPIES IN ELDERLY PATIENTS WITH ULCERATIVE COLITIS

This chapter is presented as a manuscript submitted for publication in Alimentary Pharmacology & Therapeutics "Gastroenterologists' Preference on the Use of Immunomodulators and Biological Therapies in Elderly Patients with Ulcerative Colitis – an International Survey"

Gastroenterologists' Preference on the Use of Immunomodulators and Biological Therapies in Elderly Patients with Ulcerative Colitis – an International Survey

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Non-standard Abbreviations: - None

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6.1 Abstract

Background and aims

Increased risk of comorbidity, polypharmacy, malignancy and infection complicates drug treatment of elderly patients with inflammatory bowel diseases (IBD). Age, therefore, might influence a physician's preference in the prescription of immunosuppressive therapies or surgery.

Methods

A case-based survey was conducted worldwide assessing gastroenterologists' selection of drug treatments based on patients' comorbidity and age in the management of moderate-to-severe ulcerative colitis (UC). Primary aim was to assess gastroenterologists' decision to prescribe medical treatment versus colectomy in elderly UC patients, and identify the factors associated with their choices using logistic regression analysis.

Results

A total of 424 respondents from 41 countries were included. Vedolizumab (53.2%) and thiopurines (19.4%) were the top treatment preferences for moderate-to-severe UC ($p<0.0001$). Comorbidity reduced the probability of prescribing immunomodulators for elderly- (odds ratio (OR): 0.25, 95% confidence interval (CI): 0.16-0.38, $p<0.001$) and for younger-patients (OR: 0.56, 95%CI: 0.39-0.82, $p<0.001$) compared to elderly patients without comorbidities. Conversely, elderly- and younger-patients with comorbidities were more likely to receive vedolizumab (OR: 2.71, 95%CI: 1.98-3.71, $p<0.0001$, and OR: 1.37, 95%CI: 1.01-1.86, $p=0.04$, respectively) and colectomy (OR: 5.40, 95%CI: 2.74-10.64, $p<0.0001$, and OR: 4.46, 95%CI:2.25-8.87, $p<0.0001$, respectively]. 93.9% of respondents considered that patient age was not a limit for vedolizumab, while 37.9% considered age as a limiting factor in prescribing thiopurines ($p<0.001$)).

CONCLUSIONS

Patient comorbidity is a major determinant in the selection of medical and surgical therapy, rather than age alone in moderate-to-severe UC. There is worldwide acceptance of vedolizumab as the drug of choice in elderly IBD.

6.2 INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is increasing in incidence and prevalence globally across all age groups [1][2]. Elderly IBD patients include those diagnosed at a younger age who transition to an elderly age, and those diagnosed after the age of 60 years (elderly-onset IBD) [3]. Approximately 25-35% of IBD patients are over the age of 60 years, with 10-15% of these with elderly-onset IBD [4-6]. With the aging population, IBD prevalence also increases with age and peaked at 1,061 per 100,000 in patients >85 years old [7].

Conventional IBD therapy consists of mesalazine, corticosteroids, and the immunomodulators thiopurine and methotrexate. In the past two decades, biological agents have led a paradigm shift in the management of IBD. Anti-tumour necrosis factor (TNF)-α agents (infliximab [8]-[11], adalimumab [12]-[16], certolizumab pegol [17][18], and golimumab[19][20]), as well as anti-integrin agents (vedolizumab) [21][22] were approved for induction and maintenance therapy in both moderate-to-severe CD and UC. More recently, ustekinumab [23] and tofacitinib [24] have been added. Most pivotal studies excluded the recruitment of elderly patients, therefore, efficacy and safety data of these drugs in the elderly is deficient. Despite increased risk of hospitalisation, surgery, post-surgical complications and steroid dependency [25]-[28] associated with elderly IBD, immunomodulators and biological agents are underutilized with dependence on steroid and mesalazine maintenance for its management [29][30]. Moreover, elderly IBD patients often have comorbidities, polypharmacy with potential for drug interactions, medication adherence issues, which may further complicate the management of this group of patients [30][31].

Currently there are no age-specific treatment guidelines for IBD in the elderly **[3]**. Therefore, the attending physicians' preferences, knowledge and attitude towards the use of immunomodulators and biological agents in the elderly may influence prescription practice. We therefore conducted

a survey to determine the preference of gastroenterologists on the decision to prescribe medical treatment versus colectomy in elderly IBD patients, and the factors associated with their choices. Secondary aims were to identify conditions that preclude gastroenterologists from prescribing immunomodulators and biological agents, and whether patient age is considered a limitation to prescribing these medication classes.

6.3 Materials and methods

Survey design

This investigator-initiated study was conducted in collaboration with two operational boards of the European Crohn's and Colitis Organisation (ECCO): Young-ECCO (Y-ECCO) and the clinical committee of ECCO (ClinCom). The decision to support this proposal was made by these committees through an independent review board following an international call to submit projects. The first version of the survey was designed by VK, SK and RL, and reviewed by Y-ECCO, ClinCom and the members of the ECCO governing board. After two rounds of modifications, the final version of the survey was approved by consensus. The survey consisted of 17 questions and was divided into four categories. First, gastroenterologists' demographics, including medical position, continent and country of practice, years in gastroenterology practice, number of IBD patients reviewed per week, and practice type, were collected. Second, we devised three clinical scenarios to determine gastroenterologists' preference on the use of immunomodulators and biological therapies in elderly IBD patients. Third, we assessed the conditions that precluded gastroenterologists from prescribing the immunomodulators and biologic agents. Fourth, the age limits of ordering such medications were recorded. The estimated time to complete the survey was 5 minutes. (Supplement 1).

THE CASE SCENARIOS

Three case scenarios were designed to assess the impact of elderly-age alone, elderly-age with comorbidities and younger-age with comorbidities.

The first case scenario was a 76-year-old female with steroid-refractory UC, despite adherence to oral mesalazine 4g daily. She required 3 courses of oral corticosteroids over a 9-month period (Supplement 1). Her colonoscopy revealed extensive colitis with Mayo endoscopic sub score of 3. The patient had no other comorbidity. Scenario 2 was similar to the first one, but the patient had comorbidities of type 1 diabetes mellitus with diabetic nephropathy and ductal adenocarcinoma of the left breast in remission. Scenario 3 was identical to the scenario 2 but the patient was now 28 years old.

All three case scenarios included 5 treatment options including prescribing immunomodulators, high dose maintenance corticosteroids, mono- or combination therapy with anti-TNF, mono- or combination therapy with vedolizumab, and colectomy. The participants were asked to rank their 5 choices of treatment, with 1 the most preferred and 5 the least.

STUDY POPULATION

The survey was first distributed anonymously in hard copy format amongst participants at a gastroenterology conference in Australia and the ECCO conference in February 2017. Thereafter, the questionnaire was deployed in an online platform (SurveyMonkey), using a viral networking technique to further increase the reach of the survey beyond those initially targeted. Gastroenterologists from the Asian Organization for Crohn's & Colitis [AOCC], Belgian Intestinal Research and Development [BIRD], British Society of Gastroenterology [BSG], Grupo Español de

Trabajo de Crohn y Colitis Ulcerosa [GETECCU], Italian Group for the study of IBD [IG-IBD] were also invited through emails to participate into the survey.

The inclusion criteria were adult gastroenterologists that consulted ≥2 IBD patients per week and completed >50% of the questionnaire. Gastroenterologists who cared for two or more IBD patients per week were pragmatically defined as IBD specialists. The anonymous survey was approved by the Centralised Institutional Review Board of SingHealth Research(CIRB Reference number: 2019/2056) and completion and return of the survey was considered informed consent.

STATISTICAL ANALYSIS

Standard descriptive statistics summarized demographic data and overall responses for each question. Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as medians and interquartile range [IQR]. Comparison of responses between groups was by chi-square test, Kruskal-Wallis H test, and ANOVA t test, as appropriate. Univariate and multivariate binary logistic regression was used to determine variables associated with each treatment choice. Variables with a p-value of <0.05 in univariate analysis were included in to multivariate analysis. Results are expressed as odds ratios (OR) and their 95% confidence intervals (95% CI). Statistical analyses were conducted using SPSS [IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA)].

6.4 RESULTS

STUDY COHORT

The questionnaire was distributed in 41 countries covering five continents. The precise questionnaire return rate was an estimate based on the return rate of the survey handouts at major conferences and the online survey website. Based on our best estimate, a response return rate of 80% was received.

A total of 550 gastroenterologists responded to the survey, of whom 424 physicians met the inclusion criteria (Figure 6.1). Characteristics of the gastroenterologists included are depicted in Table 6.1 (and Supplement 2). Of those surveyed, 43.9% (n = 186) were from Europe, 23.3% (n = 99) from Asia, and 22.6% (n = 96) from Oceania with a median of 12 years (IQR: 5.0–20.75 years) of experience in gastroenterology. Most IBD specialists worked in public hospitals (68.6%) and 67.5% of all respondents treated >10 IBD patients per week.

RESPONSE TO CASE SCENARIOS

Vedolizumab was the most preferred treatment choice in all 3 case scenarios, with 43.9%, 64.9 and 50.9% selecting it as the first choice for cases 1, 2 and 3 respectively (Table 6.2). Immunomodulators was the second choice overall, being recommended as the first choice by 28.5%. 10.9% and 18.7% for cases 1, 2 and 3 respectively. Comorbidity was the decisive factor in selecting colectomy over age. Overall, 13.3% of respondents selected colectomy as the preferred option for the elderly with comorbidity, 11.5% for the young patient with comorbidity, while only 2.8% of gastroenterologists selected colectomy for the elderly without comorbidity ($p<0.0001$). Overall, Only 2.7% of respondents selected increasing the dose and maintaining prednisolone as the preferred maintenance treatment.

FACTORS ASSOCIATED WITH TREATMENT CHOICES

On multivariate analysis, the presence of comorbidity was associated with a lower probability of prescribing immunomodulators. The probability of prescription of thiopurines in elderly patients with comorbidities (OR: 0.25, 95%CI: 0.16-0.38, p<0.001) and young patients with comorbidities (OR: 0.56, 95%CI: 0.39-0.82, p=0.001) was lower compared to elderly patients without comorbidities (Table 6.3). European and North American physicians had a significantly lower probability of prescribing immunomodulators than Asian physicians (OR:0.52, 95%CI 0.34-0.80, p=0.003 and OR: 0.03, 95%CI; 0.004-0.22, p=0.001) respectively. As expected, having a perceived age limit to prescribing immunomodulators was associated with lower probability of prescribing immunomodulators (OR: 0.43, 95%CI: 0.28-0.66, p<0.0001). On the other hand, having an age limit to prescribing biological therapies was associated with a higher probability of prescribing immunomodulators (OR: 1.74, 95%CI: 1.04- 2.90, p=0.034, and OR: 3.34, 95%CI: 1.70-6.54, p<0.0001 for anti-TNF and vedolizumab respectively).

In the elderly, the presence of comorbidities significantly decreased the likelihood of prescribing an anti-TNF (OR: 0.28, 95%CI: 0.17-0.46, p<0.0001). More experienced physicians (OR: 0.98, 95%CI: 0.96-0.99, p=0.017) and those seeing a higher number of IBD patients per week (OR 0.50, 95%CI 0.31-0.79, p=0.003) were less likely to prescribe anti-TNF.

The presence of comorbidities increased the likelihood of preferring vedolizumab as first option, for both elderly- (OR: 2.71, 95%CI: 1.98-3.71, p<0.0001) and younger patients (OR: 1.37, 95%CI: 1.01-1.86, p=0.04) compared to the elderly patient without comorbidity. Gastroenterologists who saw a higher number of IBD patients per week (OR: 1.90, 95%CI: 1.35 – 2.69, p<0.0001) and North American physicians compared against Asia (OR: 5.59, 95%CI: 2.96-10.53, p<0.0001) were more likely to prescribe vedolizumab. Having a perceived age limit for prescribing thiopurines was associated with higher likelihood of using vedolizumab (OR: 1.51, 95%CI: 1.15-1.99, p=0.003).

On multivariate analysis, the presence of comorbidities was the only independent predictor for selecting colectomy and this was irrespective of age. Elderly patients with comorbidities (OR: 5.40, 95%CI: 2.74-10.64, p<0.0001) and younger patients with comorbidities (OR: 4.46, 95%CI: 2.25-8.87, p<0.0001) had significantly higher probability of having colectomy than elderly patients without comorbidities. Perceived age barrier in the prescription of vedolizumab was also associated with a higher probability of selecting colectomy (OR: 2.95, 95%CI: 1.37-6.32, p=0.006). Corticosteroid use was not associated with age or comorbidities (Supplement 3).

CONDITIONS PRECLUDING IMMUNOMODULATORS AND BIOLOGICAL AGENTS IN ELDERLY PATIENTS WITH IBD

History of lymphoma (94%) and opportunistic infection (78.3%) were most frequently reported as conditions precluding the use of thiopurine and anti-TNF in elderly IBD patients respectively (Table 6.4). Opportunistic infection (57.4%) was the commonest condition considered as contraindications to vedolizumab in elderly IBD patients.

AGE LIMIT FOR PRESCRIBING IMMUNOMODULATORS AND BIOLOGICAL THERAPY

Vedolizumab and corticosteroids were prescribed without an age limit by 93.9% and 93.7% respondents respectively. However, 37.9% of gastroenterologists considered age as a limiting factor in prescribing thiopurines (Figure 6.2).

6.5 DISCUSSION

This is the first global survey that examined therapeutic options made on UC patients and factors relating to these decisions. The presence of comorbidity was the single most important factor

associated with this decision-making process rather than age. Surgery was also recommended to patients based on the presence of comorbidity and not age. These findings are in accordance with recommendations made by the 'European Crohn's and Colitis Organisation Topical Review on IBD in the Elderly' that recommended management decisions to be made based on patients' frailty rather than their chronological or biological ages [3]. Around 40% of gastroenterologists avoided prescribing thiopurines for patients >50 years old, while majority of IBD specialists, did not consider an age limit for prescribing vedolizumab. The topic of patients' age, as a limit for prescribing immunomodulators and biological therapies has not been studied in an IBD population before. In clinical trials for infliximab [8]-[11] and golimumab [19][20], no upper age limit was set. For certolizumab [17][18], adalimumab [12]-[16], and vedolizumab [21][22], the upper age limits were 65, 75 and 80 years, respectively. In a recent meta-analysis, the absolute risk of lymphoma in IBD patients treated with thiopurines was highest in patients >50 years old (1:354 cases per patient-year, with a relative risk of 4.78) [40]. This could potentially explain the age limit of thiopurine prescription observed in this study.

The ageing population and rising incidence of IBD contribute towards the increasing prevalence of elderly IBD patients [3]. Presence of comorbidity and polypharmacy in elderly patients further underpins the challenges associated with managing this population at risk of opportunistic infections and cancers [32][33]. The influence of comorbidity on treatment choices is poorly researched. Kariyawasam et al[31] recently reported the impact of comorbidity in the use of immunomodulators in a comparative study of elderly and younger onset IBD patients. Charlson's Comorbidity Index was significantly associated with lower probability of prescribing immunomodulators, in CD (Hazard ratios (HR): 0.86, 95%CI: 0.79-0.95) and UC (HR: 0.81, 95%CI: 0.71-0.92)[30]. Age of diagnosis was not an independent predictor of Immunomodulator use [31].

According to the consensus guidelines of the European Crohn's and Colitis Organisation for the treatment of UC [35], patients with steroid-dependency of at least moderate severity should be treated with a thiopurine, anti-TNF (preferably combined with a thiopurine), vedolizumab, or methotrexate. Our survey identified that vedolizumab ranked first among the five choices in all 3

scenarios. Comorbidity, but not age, was independently associated with the selection of vedolizumab as the treatment option. A recently published study on real world experience of vedolizumab, demonstrated safety in the elderly [36]. There are limited data to demonstrate the safety of vedolizumab in subjects with comorbidity. Through its targeted, gut selective mechanism of action, however, vedolizumab is an attractive option in the elderly and in patients with comorbidities. Our survey confirms that prednisolone is to be avoided as maintenance medication in the elderly. However, some real-world data demonstrate high rates of prednisolone usage as maintenance therapy [37][38].

The presence of comorbidity was the single most important factor in influencing the decision in recommending colectomy. Colectomy, whilst sometimes viewed as being a curative option in UC, mostly results in the cessation of all immunomodulator and biological drugs. However, this decision must be balanced against the increased rate of postoperative morbidity and mortality in operative subjects aged over 60 years with comorbidities [26-28][39]. Recent population-based studies demonstrated higher surgical rates in elderly-onset UC compared to young-onset UC patients. The increased surgical rate was associated with very low immunomodulator use. Therefore, the decision to perform colectomy might have been driven by the treating physician's decision to select colectomy to avoid medical therapy, rather greater severity of the patients' UC. Conversely the lower rate of use of immunomodulator in the elderly also represented the physicians' choice.

Lymphoma was regarded as the major contraindication to thiopurines in elderly patients. Following the diagnosis of a solid organ cancer, as many as 2-3 times more gastroenterologists would stop thiopurines (65.1%) or anti-TNF agents (57.4%) than vedolizumab. Overall, the prescribing pattern from the 3 scenarios suggest that vedolizumab has emerged as the first line therapy for elderly patients with moderate-to-severely active UC, with or without comorbidity, and in patients with significant comorbidities of any age. There was a surprisingly high proportion

of respondents to this survey that did not avoid using anti-TNF in the presence of demylination, recent melanoma or congestive heart failure.

The strength of the study is the large sample size of gastroenterologists from across the world to reflect the global practice pattern of the IBD specialists on the use of immunomodulators and biological agents in the elderly IBD population. It shows the emerging trend of selecting vedolizumab in all countries where that drug has been launched. The longer the country has had approval for vedolizumab, the greater the preference is for its use in UC patients with comorbidities. There are some limitations in our study. Firstly, due to the recruitment across multiple countries, the absolute number of gastroenterologists were relatively small in certain countries. This could affect the generalisability of the study results globally. However, when analysing on a per-continent basis, there was consistency in the results across country-groups with the main differences being countries that had vedolizumab longer tended to select this as an option over thiopurines. Secondly, selection bias might also be present through only those with interest in managing IBD responding. However, we tried to invite survey respondents not only from IBD conferences but by emailing survey links to increase the variety of respondents. We also analysed subjects according to the numbers of IBD cases seen per week to determine whether IBD expertise drove their survey responses. Thirdly, we did not explore other IBD populations or phenotypes in this survey such as pediatric subjects, luminal Crohn's disease or perianal Crohn's disease, which might reduce the choice of vedolizumab as a preferred option. However, this was to keep the survey simple and easy to complete. We also limited the IBD phenotype to UC to ensure consistency across the 3 scenarios and isolating age and comorbidities as independent variables. Fourthly, we did not explore newer treatment options such as ustekinumab [23] and tofacitinib [24]. However, at the time of the survey ustekinumab was not yet available in most parts of the world and there were no data available for its use in UC.

In conclusion, comorbidity was the major determinant in the selection of either medical or surgical therapy in moderate-to-severe UC, whereas patient age alone was not. Vedolizumab has emerged

as the preferred first line agent worldwide, in the treatment of elderly IBD patients with moderate-to-severe ulcerative colitis refractory to corticosteroids, with or without comorbidity, and in younger patients with comorbidity. In elderly IBD patients, the presence of opportunistic infection and lymphoma were the main barriers in prescribing biological therapies and thiopurines, respectively. Around 40% of gastroenterologists avoided prescribing thiopurines for patients >50 years old, while majority of IBD specialists, did not consider an age limit for prescribing vedolizumab.

Table 6.1 Gastroenterologists' Demographic and Clinical Characteristics

Gastroenterologists' Characteristics	**N = 424 (%)**	
Continent		
Asia	Total = 99 (23.3%)	
Australia and Oceania	Total = 96 (22.6%)	
Europe	Total = 186 (43.9%)	
North America	Total = 35 (8.3%)	
South America	Total = 8 (1.9%)	
Years in practice		
Median (years (IQR))	12	(IQR 5 – 20.75)
<5 years	98	(23.1)
6-10 years	77	(18.2)
11 – 15 years	60	(14.2)
>15 years	152	(35.8)
Missing	37	(8.7)
Number of IBD patients seen per week		
2-5 patients	78	(18.6)
6-10 patients	59	(13.9)
>10 patients	286	(67.5)
Practice setting		
Public	291	(68.6)
Private	56	(13.2)
Mixed (public + private)	76	(17.9)
Missing	1	(0.2)

Table 6.2 First Choices of Treatment Based on Case Scenarios

	Case Scenarios				
First Choice of Treatment	Elderly (Case 1)	Elderly with comorbidity (Case 2)	Young with comorbidity (Case 3)	Overall	p value
Prescribe Immunomodulators	28.5% (113/396)	10.9% (43/394)	18.7% (73/390)	19.4%	P<0.0001
Increase dose of prednisolone and continue on that dose for maintenance	3.0% (7/397)	3.0% (12/395)	2.1% (8/389)	2.7%	P=0.622
Prescribe Anti-TNF	23.8% (95/400)	8.8% (35/396)	18.3% (72/394)	17.0%	P<0.0001
Prescribe Vedolizumab	43.9% (175/399)	64.9% (259/399)	50.9% (200/393)	53.2%	P<0.0001
Colectomy	2.8% (11/397)	13.3% (53/399)	11.5% (45/393)	9.2%	P<0.0001

Table 6.3 Multivariate Logistic Regression Analysis of Variables Associated With the selection of treatment options as first line treatment

Covariates	Immunomodulators		Anti-TNF		Vedolizumab		Surgery	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Scenario								
Scenario 1	1		1		1		1	
Scenario 2	0.25 (0.16-0.38)	<0.0001	0.28 (0.17-0.46)	<0.0001	2.71 (1.98-3.71)	<0.0001	5.40 (2.74-10.64)	<0.0001
Scenario 3	0.56 (0.39-0.82)	0.003	0.70 (0.48-1.04)	0.76	1.37 (1.01-1.86)	0.043	4.46 (2.25-8.87)	<0.0001
Continent								
Asia	1		1		1		1	
Oceania	1.15 (0.73-1.81)	0.55	0.72 (0.41-1.26)	0.249	1.44 (0.099-2.09)	0.53	0.53 (0.25-1.10)	0.088
Europe	0.52 (0.34-0.80)	0.003	1.55 (0.98-2.45)	0.61	1.23 (0.89-1.69)	0.21	1.41 (0.85-2.33)	0.182
North America	0.03(0.004-0.022)	0.001	0.67 (0.29-1.55)	0.35	5.59 (2.96-10.53)	<0.0001	0.56 (0.21-1.54)	0.265
South America	0.25 (0.03-2.02)	0.197	3.97 (1.34-11.82)	0.013	0.56 (0.20-1.56)	0.269	0.41 (0.05-3.48)	0.413
Years as gastroenterologist (in years)	*		0.98 (0.96-0.99)	0.017	*		*	
Number of IBD patients reviewed per week	*						*	
2-5			1		1			
6-10			0.76 (0.42-1.37)	0.36	1.03 (0.66-1.61)	0.88		
>10			0.50 (0.31-0.79)	0.003	1.90 (1.35-2.69)	<0.0001		
Place of Practice			*		*			
Public	1						1	
Private	1.69 (1.05-2.73)	0.031					0.46 (0.20 -1.07)	0.072
Mixed	1.25 (0.81-1.04)	0.312					0.51 (0.26 -1.01)	0.054
Age limit for thiopurines	0.43 (0.28-0.66)	<0.0001	*		1.51 (1.15-1.99)	0.003	*	
Age limit for vedolizumab	3.34 (1.70-6.54)	<0.0001	*		0.24 (0.12-0.48)	<0.0001	2.95 (1.37 - 6.32)	0.006
Age limit for anti-TNF	1.74 (1.04-2.90)	0.034	*		0.72 (0.49-1.04)	0.082	1.66 (0.98 – 2.81)	0.057
Age limit for Steroids	0.32 (0.13-0.80)	0.014	2.02 (1.05-3.91)	0.036	*	*	*	
Age limit for combination therapy	0.68 (0.45-1.01)	0.056	*		*		*	

* Factors not statistically significant on univariate analysis
OR – odds ratio, CI – confidence interval, p – p value

Table 6.4 Conditions precluding the use of immunomodulators and biological agents in elderly patients with IBD

Conditions	Preclude commencing medications (% from respondents within the drug)				
	Missing input (% of total)	Immuno-modulator	Anti TNF	Vedolizumab	p value
History of lymphoma	16	94.0	69.0	30.4	<0.0001
History of solid organ cancer	5.7	65.1	57.4	20.0	<0.0001
Melanoma skin cancer	16.3	44.7	61.0	20.6	<0.0001
Non-melanoma skin cancer	14.3	53.2	29.2	13.6	<0.0001
Congestive heart failure	16.1	5.3	76.6	12.1	<0.0001
Demyelination	14.2	7.8	61.8	19.5	<0.0001
Osteoporosis	16.3	1.5	1.0	0.7	0.627
Hepatotoxicity	5.8	69.1	22.2	19.1	<0.0001
Opportunistic infection	16.2	72.6	78.3	57.4	<0.0001
Drug to drug interaction	14.5	52.3	31.4	38.2	<0.0001

Figure 6.1 Flow diagram showing the recruitment of gastroenterologist globally

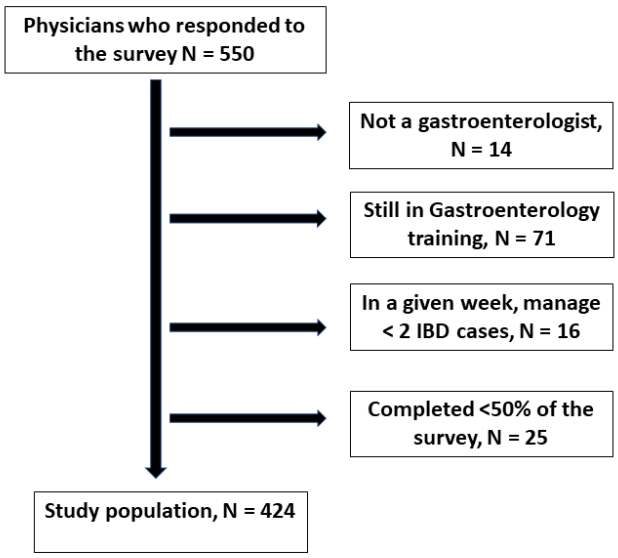
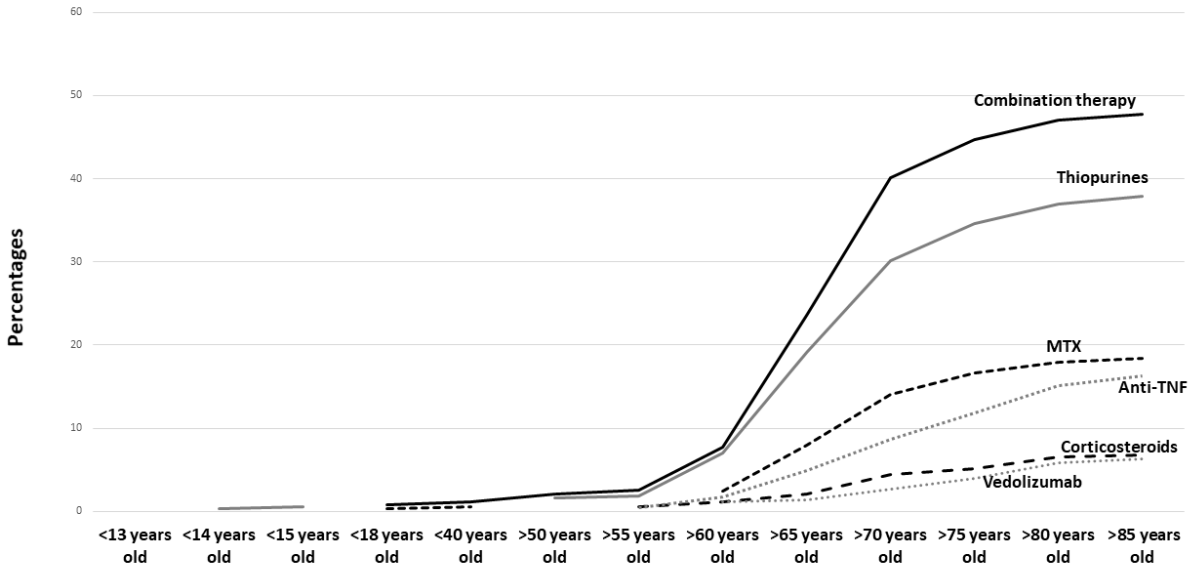


Figure 6.2 Cumulative percentage of gastroenterologists who have age limits for prescribing immunomodulators and biological agents.



Supplement 6.1: Questionnaire

Gastroenterologists' Preference on the Use of Immunomodulators and Biological Therapies in Elderly Patients with Ulcerative Colitis

Physician Demographics

(a) Current medical position:

□ Gastroenterologist □ Fellow □ Registrar □ Resident □ Other: _____

(b) Country of practice: _____

(c) Year Gastroenterology specialist qualification obtained (if applicable): _____

(d) Average number of IBD patients seen per week:

□ 0-1 patient □ 2-5 patients □ 6-10 patient □ >10 patients

(e) Where is your primary place of practice?

□ Public hospital □ Private practice □ Mixed practice

SCENARIO 1

A **76 year old** female with **extensive ulcerative colitis** has been in remission and adherent on mesalazine 4g a day. She has, however, required 3 courses of prednisolone in the past 9 months for symptomatic flares (abdominal pain, bloody diarrhoea). Colonoscopy showed **Mayo 3 pancolitis** (erosions, superficial ulceration). She has been **on steroids for 3 months** and has weaned down to 10mg of prednisolone and continues to experience diarrhoea with urgency. The patient has no other comorbidity. How would you treat this patient? *(Please place in order 1 to 5 with 1 = most preferred option, 5 = least preferred option)*

☐ Prescribe azathioprine or mercaptopurine; but no biological agent

☐ Increase dose of prednisolone and continue on that dose for maintenance

☐ Prescribe infliximab, adalimumab or golimumab (with or without an immunomodulator)

☐ Prescribe vedolizumab (with or without an immunomodulator)

☐ Recommend colectomy

SCENARIO 2

If the same patient also has **Type 1 Diabetes Mellitus** with **diabetic nephropathy** (serum creatinine 135μmol/L) and a history of **ductal adenocarcinoma of left breast** treated with mastectomy and chemo-radiotherapy 2 years ago **without recurrence at present**. How would you treat this patient?

(Please place in order 1 to 5 with 1 = most preferred option, 5 = least preferred option)

☐ Prescribe azathioprine or mercaptopurine; but no biological agent

☐ Increase dose of prednisolone and continue on that dose for maintenance

☐ Prescribe infliximab, adalimumab or golimumab (with or without an immunomodulator)

☐ Prescribe vedolizumab (with or without an immunomodulator)

☐ Recommend colectomy

SCENARIO 3

The patient is now a **28 year old** female with similar presentation as **Scenario 2.** How would you treat this patient? *(Please place in order 1 to 5 with 1 = most preferred option, 5 = least preferred option)*

☐ Prescribe azathioprine or mercaptopurine; but no biological agent

☐ Increase dose of prednisolone and continue on that dose for maintenance

☐ Prescribe infliximab, adalimumab or golimumab (with or without an immunomodulator) Prescribe vedolizumab

☐ (with or without an immunomodulator)

☐ Recommend colectomy

Managing Elderly Patients with IBD

(a) Which conditions would stop you from commencing a 70 year old patient on **azathiopurine, mercaptopurine or methotrexate**? (Tick all that apply)

□ Lymphoma	□ Demyelination
□ Solid organ cancer	□ Osteoporosis
□ Melanoma skin cancer	□ Hepatotoxicity/nephrotoxicity
□ Non-melanoma skin cancer	□ Opportunistic infections
□ Congestive heart failure	□ Drug-to-drug interactions

(b) Which conditions would stop you from commencing a 70 year old patient on **anti-TNF agent**? (Tick all that apply)

□ Lymphoma	□ Demyelination
□ Solid organ cancer	□ Osteoporosis
□ Melanoma skin cancer	□ Hepatotoxicity/nephrotoxicity
□ Non-melanoma skin cancer	□ Opportunistic infections
□ Congestive heart failure	□ Drug-to-drug interactions

(c) Which conditions would stop you from commencing a 70 year old patient on **vedolizumab**? (Tick all that apply)

□ Lymphoma	□ Demyelination
□ Solid organ cancer	□ Osteoporosis

□ Melanoma skin cancer
□ Non-melanoma skin cancer
□ Congestive heart failure
□ Hepatotoxicity/nephrotoxicity
□ Opportunistic infections
□ Drug-to-drug interactions

(d) Starting at what patient age would you **NOT** prescribe the following drugs?

I never start **corticosteroid** in a patient of age >_____ / I have no age barrier.

I never start **azathioprine/mercaptopurine** in a patient of age >_____ / I have no age barrier.

I never start **methotrexate** in a patient of age >_____ / I have no age barrier.

I never start **anti-TNF agent** in a patient of age >_____ / I have no age barrier.

I never start **corticosteroid** with **anti-TNF** with **azathioprine/mercaptopurine** in a patient of age >_____ / I have no age barrier.

I never start **vedolizumab** in a patient of age >_____ / I have no age barrier.

<END OF QUESTIONNAIRE>

Supplementary table 6.2. Gastroenterologists' Demographic and Clinical Characteristics

Gastroenterologists' Characteristics		N = 424 (%)		
Continent	Country of residence			
Asia	China	5	(1.2)	
	Hong Kong	1	(0.2)	
	India	4	(0.9)	
	Indonesia	2	(0.5)	
	Israel	5	(1.2)	
	Japan	18	(4.2)	Total = 99 (23.3%)
	Korea	9	(2.1)	
	Kuwait	3	(0.7)	
	Malaysia	1	(0.2)	
	Saudi Arabia	2	(0.5)	
	Singapore	5	(1.2)	
	Taiwan	5	(1.2)	
	United Arab Emirates	1	(0.2)	
	Missing	38		
Oceania	Australia	93	(21.9)	Total = 96 (22.6%)
	New Zealand	3	(0.7)	
Europe	Austria	3	(0.7)	
	Belgium	9	(2.1)	
	Bulgaria	1	(0.2)	
	Croatia	1	(0.2)	
	Czech Republic	16	(3.8)	
	Denmark	1	(0.2)	
	Finland	3	(0.7)	
	France	5	(1.2)	
	Germany	6	(1.4)	
	Greece	18	(4.2)	Total = 186 (43.9%)
	Hungary	2	(0.5)	
	Ireland	5	(1.2)	
	Italy	15	(3.5)	
	Netherlands	2	(0.5)	
	Poland	6	(1.4)	
	Portugal	1	(0.2)	
	Serbia	1	(0.2)	
	Slovakia	1	(0.2)	
	Spain	14	(3.3)	
	Sweden	11	(2.6)	
	Switzerland	4	(0.9)	
	Missing	61		
North America	Canada	5	(1.2)	Total = 35 (8.3%)
	USA	15	(3.5)	
	Missing	15		
South America	Brazil	4	(0.9)	Total = 8 (1.9%)
	Colombia	4	(0.9)	
Years in practice				
Median (years (IQR))		12	(5 – 20.75)	
Number of IBD patients seen per week				
2-5 patients		78	(18.6)	
6-10 patients		59	(13.9)	
>10 patients		286	(67.5)	
Practice setting				
Public		291	(68.6)	
Private		56	(13.2)	
Mixed (public + private)		76	(17.9)	
Missing		1	(0.2)	

Supplement table 6.3. Multivariate Logistic Regression Analysis of Variables Associated With the selection of corticosteroids as first line treatment

Covariant considered in univariate analysis	Corticosteroids	
	OR (95% CI)	p value
Scenario • Scenario 1 • Scenario 2 • Scenario 3	*	
Continent • Asia • Oceania • Europe • North America • South America	Removed from the model	0.645
Years as gastroenterologist (in years)	*	
Number of IBD patients reviewed per week • 2-5 • 6-10 • >10	*	
Place of Practice • Public • Private • Mixed	Removed from the model	0.090
Age limit for thiopurines	*	
Age limit for vedolizumab	3.66 (1.27 – 10.56)	0.016
Age limit for anti- TNF	*	
Age limit for Steroids	6.61 (2.70- 16.19)	<0.0001
Age limit for combination therapy	*	
* Factors not statistically significant on univariate analysis OR – odds ratio CI – confidence interval		

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CHAPTER 7 SUMMARY AND CONCLUSIONS

7.1 CONCEPTS AND CONTEXT OF THIS THESIS

Over the past two decades, the advent of monoclonal biologic agents has revolutionized IBD treatment (115). The list of drugs available is ever growing, providing patients and treating physicians more therapeutic options (116). However, a significant proportion of patients do not respond to these drugs or lose response over time (117). The long-term adverse events of these therapies are not yet accurately known.

Furthermore, these therapies come at an exceptionally high financial cost. For example, cost of treating a patient with azathioprine is a fraction of the cost needed to prescribe biologic monotherapy; azathioprine costs between 21 and 25 euros for 3 months therapy while infliximab and adalimumab cost between 412 and 570 euros and 427 and 629 euros per patient respectively, in the Netherlands(118). Therefore, with increasing incidence and increasing healthcare costs, affordability of these drugs is a concern in both the developing and developed world (14).

Conventional IMs, particularly thiopurines, have been utilized in the treatment of IBD for more than 50 years, allowing estimation of its efficacy, safety and impact on hard clinical end points like surgery. Long term adverse events related to IM use, especially in the elderly, are well documented(106,119). Risk of intestinal surgery has decreased over the past 6 decades, associated with an increased earlier use of immunomodulators(120,121). However, most population-based studies have failed to demonstrate beneficial effect of immunomodulators in reducing surgical risk, due to treatment selection bias in patients with severe phenotypes or due to the delay in commencing the treatment(120). Additionally, two recent randomized controlled trials also failed to prove a beneficial effect of thiopurines (31,32). However, both these studies were poorly designed and were not able to assess the long-term outcomes. Both studies had relatively small sample size with limited follow-up and a high proportion of control subjects eventually required commencement of thiopurines, which may negate any benefit. In addition, they were designed to assess the short term impact of thiopurines, which are recognized to fail, be complicated by drug-induced idiosyncratic and dose-related adverse effects or not tolerated in up to 40% of patients (33).

These results may have led to questions regarding the utility of conventional IMs in the treatment of IBD in the recent years. On the other hand, the use of IMs has been found to positively influence the outcome of patients on infliximab and decrease its immunogenicity **(85).** Whether IMs have the same effect on the less immunogenetic biologics like adalimumab is not known.

Our understanding of thiopurine metabolism has improved over the last decade. By testing for TPMT gene mutations, using therapeutic drug monitoring and managing shunting with allopurinol, we have been able to optimize therapy and reduce adverse events. Therefore, filling the gaps in our knowledge about the efficacy of IMs and the contributing factors affecting their efficacy and their prescription will help us develop strong recommendations on the use of IMs, particularly thiopurines, in the treatment of IBD.

The common aim of this doctoral program was to address some of these gaps and help to define the role of thiopurines in the modern treatment algorithm of IBD. Individual studies were conducted to assess the role of thiopurines in the long-term surgical outcome of CD and UC and its role as a concomitant immunomodulator with adalimumab in the treatment of CD. A further study was conducted to assess its utility in elderly IBD and outcomes related to thiopurine use in this increasing patient sub-group. We also assessed the physician's knowledge, attitude and preferences in the use of IMs in elderly.

7.2 Summary of findings

Intestinal surgery is considered as a robust hard endpoint when assessing efficacy of drug treatments in IBD. It is hard to assess these long tern endpoints using randomised controlled studies. Similarly, assessing these endpoints using population-based data is also difficult due to inherent issues related to possible treatment selection bias and changes in practice over time.

These issues are clearly seen in an earlier study published from Cardiff, which did not account for these biases **(122).** Lakatos et al, reported a similar reduction in surgery associated with early introduction of azathioprine that was independent of the decade of diagnosis. We, for the first time using real life management protocols, have shown the benefit of early immunomodulator strategy in CD, in reducing the risk of major abdominal surgery. To eliminate drug selection bias, we used a strict propensity score matching.

Using similar methodologies to eliminate possible biases, we also demonstrated significant benefit of early IMs post initial surgery in CD in preventing further intestinal surgeries. Despite multiple clinical trials demonstrating benefits of thiopurines in preventing postoperative recurrence, previous population-based studies have failed to demonstrate similar benefits. **(23,39,123)**. Our study was the first population-based cohort study to demonstrate the reduced risk of perianal surgery, associated with early IM use.

Thiopurines have been used to treat UC since the 1970's. Despite a number of meta-analyses highlighting the benefits of thiopurines as maintenance of therapy for UC, most studies have failed to demonstrate benefits in reducing the risk of colectomy and disease progression**(124)**. Indirect evidence could be obtained from retrospective population-based studies, that have shown decreasing colectomy rates, while increasing rates of IM use **(30,121)**. While reporting similar findings, we also demonstrated a significant reduction in the rate of colectomy and disease progression associated with sustained use of thiopurines within five years of UC diagnosis.

Benefits of azathioprine and infliximab combination therapy is widely accepted and has been studied extensively **(125)**. However, the same is not true regarding the utility of combination therapy with adalimumab. After reviewing the existing evidence, we explored the novel theory that immunomodulators maintained for 3 months prior to starting adalimumab positively influence primary response. ADAs to adalimumab have been shown to occur as early as 2 weeks from starting therapy, and higher proportion of patients with ADAs were found in primary non-responders **(69)**. The benefits of pre-treatment IMs in reducing ADAs have been previously shown in murine models**(70)**. This may be even more relevant given the slow median time to response (3.1 months) for thiopurines**(19)**.

We demonstrated a significant increase in the primary response and lower rate of subsequent failure using this strategy. Based on our findings, we would recommend that treatment with thiopurines should be continued at least into the first 6 months after starting adalimumab to reduce the risk of failure. During maintenance, combination therapy was associated with a decrease in the proportion of flare semesters.

We also assessed the relationship between thiopurines stratified according to TGN levels and adalimumab efficacy, which has not been previously reported in literature. Subtherapeutic TGNs at induction and during maintenance therapy were associated with worse clinical outcomes and increased risk of adalimumab failure compared with patients with therapeutic TGNs.

Use of immunomodulators has been shown to be consistently low in elderly IBD patients in multiple population-based cohort studies (88,95,97,100-102). However, factors associated with the lower use of IMs in this age group have not been studied extensively. Particularly, the impact of comorbidity and polypharmacy, which are commonly found in this patient group (110), on IM use was not known. We, for the first time demonstrated that comorbidity, quantified using Charlson Comorbidity Index, to be an independent predictor of IM use, while age at diagnosis was not. We also demonstrated significantly lower immunomodulator use in the elderly compared to younger onset patients.

The rate of surgery was lower in elderly onset CD patients compared to younger onset. This is in contrast to a recent meta-analysis, which found elderly patients to have similar risk of surgical intervention (OR: 0.70, 95%CI: 0.40-1.22) compared to younger onset patients (113). Elderly onset UC patients in our study were more likely to have earlier colectomy, compared to younger onset patients, despite having similar risk of surgery at 10 years from diagnosis. Recent population-based studies have demonstrated a higher risk of colectomy in elderly UC patients, compared to the younger counterparts (97,101). Surgery for UC, however, is curative, and thus physicians and patients may prefer a more definite surgical intervention than long-term IM therapy, leading to the higher surgical rates in elderly UC patients.

Early immunomodulator therapy was associated with reduced risk of surgery in both elderly and younger onset CD patients, but it was not associated with reduced risk of colectomy in UC patients.

Our findings would support the use of early IMs therapy in healthy, elderly onset CD patients with minimal comorbidities, but not UC patients. However, further prospective studies would be required to confirm the safety and efficacy in elderly CD patients.

The study on elderly IBD, raised the possible impact of physicians' decision-making process on the use of IMs in elderly IBD and also on the colectomy rate in UC patients. However, the actual impact of age and comorbidity on decision making has been poorly studied and demonstrated in prior literature.

In chapter 6, the presence of comorbidity was found to be the single most important factor associated with the decision-making process by gastroenterologist, rather than the chronological age in our study. Our findings indicate that gastroenterologist adhere to the recently published 'European Crohn's and Colitis Organization Topical Review on IBD in the Elderly', which recommends that management decisions in elderly to be made based on patients' frailty rather than their chronological or biological ages(86). We also demonstrated that the gut selective anti-integrin monoclonal antibody Vedolizumab, is the preferred treatment option in the presence of comorbidity. However, IMs were still the second preferred treatment option in elderly without comorbidity, which could be related to the gastroenterologists understanding of safety and efficacy of IMs, availability and regulations on the prescription of biologics.

Interestingly, we found colectomy being recommended as the second preferred option in elderly UC patients with comorbidity. This may be driven by the decision to avoid long term immunosuppression, rather than based on the severity of the disease. Number of recent population-based studies have shown a higher colectomy rate in elderly UC patients, which has been interpreted as been due to severe disease phenotype. Our findings raise questions about this interpretation, as it may be simply driven by physicians' recommendations, as opposed to disease severity.

7.3 CONCLUSION AND FUTURE DIRECTIONS

Work from this thesis provides significant contribution towards the evidence supporting the use of IMs, particularly azathioprine in the treatment of IBD. These findings will strengthen the call for its continuing use in the IBD treatment paradigms for number of years to come.

The benefits shown in reducing surgery across both CD and UC, was one of the major findings of this thesis. The reduction in perianal surgery risk in CD and disease progression in UC, will require confirmation by future studies as this has not been shown in the literature before.

Utility of azathioprine with therapeutic drug monitoring for 3 months pre-adalimumab, should be recommended as standard of care to improve the primary response to these expensive drugs and also to reduce failure. However, the benefit of continuing use needs o to be balanced out based on the risks-benefit ratio of long-term combined immunosuppression(126).

In an era of thiopurine optimization with the use of therapeutic drug monitoring, aimed at reducing intolerances, shunting and failure, it would be interesting to assess these outcomes in future population-based studies. This may well confirm a permanent place for this old friend in the future treatment algorithms for IBD.

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APPENDIX

APPENDIX 1 – STUDY 1 – PUBLISHED ARTCLE

ORIGINAL ARTICLE

Early Use of Thiopurines or Methotrexate Reduces Major Abdominal and Perianal Surgery in Crohn's Disease

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Background: Earlier introduction of immunomodulators (IM) thiopurine or methotrexate is advocated to improve Crohn's disease (CD) outcomes, but whether abdominal surgery can be prevented remains controversial.

Methods: A specialist-referred cohort of CD was recruited from 1970 to 2009. Early IM use was defined as commencement of azathioprine or methotrexate within 3 years of CD diagnosis and adherence of at least 6 months. Propensity score matching was conducted to correct for confounders influencing early IM introduction. Outcomes of interest were rates of initial and recurrent major abdominal surgery for CD and their predictive factors.

Results: A total of 1035 consecutive patients with CD (13,061 patient-years) were recruited. The risk of first and recurrent major abdominal surgery at 1, 5, and 10 years were 17.5%, 28.4%, and 39.5% and 5.9%, 19.0%, and 33.3%, respectively. Early IM use increased over time from 1.3% to 55.3% ($P < 0.0001$) and was a significant independent predictor of lower rates of initial abdominal surgery (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.35–0.69), recurrent abdominal surgery (HR, 0.44; 95% CI, 0.25–0.79) and perianal surgery (HR, 0.30; 95% CI, 0.16–0.56). Using propensity score matching, early IM significantly reduced surgical rates (HR, 0.54; 95% CI, 0.37–0.79). Number needed to treat to prevent a surgical event at 5 years from diagnosis and after initial surgery was 6.99 (95% CI, 5.34–11.95) and 8.59 (95% CI, 6.26–23.93), respectively.

Conclusions: Early IM use with thiopurines or methotrexate was significantly associated with the reduced need for abdominal and perianal surgery in CD.

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Key Words: azathioprine, thiopurine, mercaptopurine, immunomodulator, methotrexate, Crohn's disease, surgery, treatment, outcome

Crohn's disease (CD) is a chronic, inflammatory gastrointestinal disorder with a high proportion of sufferers requiring abdominal surgery and recurrent surgery for relapsing disease. Intestinal resectional rates of up to 61% 5 years after the initial diagnosis have been reported.[1] A decline in surgical rates, hence possibly a change in the natural history of CD, has been associated with improved medical therapy.[2–6] Other studies, however, suggest that surgical rates have remained stable over time despite changes in medical treatment.[7–10] Most natural history studies are unable to demonstrate a positive impact of immunomodulator (IM), possibly due to their use in more severe disease, late introduction after development of strictures or fistulas, or insufficient patient-years of follow-up. Two recent randomized controlled studies demonstrated a "top-down" approach in the early introduction of thiopurines following CD diagnosis failed to reduce CD relapse compared with a convention "step-up" approach in management.[11,12] However, the sample sizes were relatively small, follow-up period too brief and a high proportion of control subjects eventually required commencement of thiopurines, which may negate any benefit. In addition, most studies have focused only on the impact of thiopurines, which are recognized to fail, be complicated by drug-induced idiosyncratic and dose-related adverse effects or not tolerated in up to 40% of patients.[13] IM therapy in CD often involves thiopurines as first-line therapy

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and methotrexate as second-line treatment after failure of thiopurines.[14,15] Therefore, to demonstrate the effectiveness of the early IM strategy on surgical outcomes, it requires a study recruiting not only those on thiopurines but also methotrexate in those intolerant to, had failed, or for whom thiopurines were contraindicated. Scrutinizing each case to ensure study definitions are met and confounding factors corrected for, is required. To these ends, a prevalence population study approach can provide the necessary case load, review of each and every case, and obtain sufficient follow-up to ensure robustness of results.[16]

Australia has one of the highest reported incidence of CD in the world with a high surgical resection rate.[17,18] Reimbursement for anti-tumor necrosis factor (TNF) alpha was unavailable until 2008, and even after that time, complete failure of at least 1 IM (or intolerance to 2 IMs) was required before commencement of anti-TNF. As such, good characterization of the effects of IM use on disease natural history is possible because of the high dependence on well-prescribed IM for their immunosuppressive and steroid-sparing effects. Additionally, Australian gastroenterologists were early adopters of thiopurine metabolite measurements and manipulation of thioguanine nucleotide levels through dose modification and addition of allopurinol for those with preferential shunting toward inactive thiopurine metabolites.[19] Methotrexate is typically used in those unsuccessfully treated with thiopurines unless contraindicated. Defined populations within Australia may therefore be an ideal setting to test the strategy of early IM use of thiopurines or methotrexate on the need for initial and recurrent surgery in CD.

Aims

The study hypothesis is that early IM use, comprising either thiopurines or methotrexate for unsuccessful thiopurine usage, reduces initial and recurrent surgical rates in CD. The primary outcome measure assessed was the cumulative probability of major abdominal surgery for CD stratified by early IM use. The secondary outcome was the impact of early IM use on requirement for recurrent major abdominal surgery and perianal surgery.

MATERIALS AND METHODS

Patient Recruitment

The "Sydney IBD Cohort" comprises a longitudinal cohort of patients first described in 1994.[20] Ambulatory patients were originally identified from histology records, pathology database, endoscopy database, medical health records, and correspondence letters from Concord Hospital, Royal Prince Alfred Hospital, and community gastroenterologists within the catchment region. The same methodology was replicated in 2010 to enrich the cohort, and the registry was updated. Diagnoses were thoroughly reviewed retrospectively using the gastroenterologists' prospective-collected electronic and written case records, endoscopy, radiology, pathology, and histology data.[21] To ensure complete data capture, only patients with a confirmed initial diagnosis of CD between January 1, 1970 and December 31, 2009 were recruited. This time period provided sufficient patient-years of follow-up of study outcomes and sufficient variation in the time to commence IM. All events occurring up until July 2012 were recorded.

Case Review and Collection of Data

Patient medical records were retrospectively reviewed for prospectively collected demographic data, disease characteristics, medication usage, and surgical history. Demographic data included age, year of diagnosis, sex, and smoking status at diagnosis. Those lost to follow-up were contacted, and if unavailable, were censored as at their last observation. Disease characteristics within 6 months of the initial diagnosis were classified according to the Montreal Classification.[22] To assess the influence of decade of diagnosis on outcomes, patients were subgrouped into Group A diagnosed between 1970 and 1979; Group B: 1980 and 1989; Group C: 1990 and 1999; and Group D: 2000 and 2009. Medical therapy included 5 aminosalicylates (5-ASA), IM (azathioprine, mercaptopurine, and methotrexate), anti-TNF therapy, and long-term corticosteroid use, defined as 6 months or more of continuous or a total of 8 months or more of discontinuous use within a 12-month period. Data on IM included time to commencement from diagnosis, side effects and duration of exposure. Early IM use was defined as introduction of IM within 3 years of diagnosis and maintained for at least 6 months.[6,23] In assessing the occurrence of recurrent surgery, the identical definition was applied for postoperative IM use with the time period commencing from the date of previous surgery. Detail of surgical procedures and resections were collected including the time to surgery. Major abdominal surgery, the primary outcome measure, was defined as intestinal resection, strictureplasty, explorative laparotomy, intra-abdominal abscess drainage, and stoma formation. Planned 2-stage operations and reversal of stoma were included in the total number of procedures but were not considered as a recurrent major surgery for analysis. Perianal surgeries consisted of abscess drainage and insertion of setons for perianal fistulae. Simple examinations under anesthesia without abscess drainage were excluded.

Treatment with IMs During the Study Period

Consistent with local practice, thiopurines were used as the first-choice IM, with azathioprine generally used ahead of mercaptopurine. Typical dosing of azathioprine was 2 to 2.5 mg/kg body weight, and for mercaptopurine it was 1 to 1.5 mg/kg body weight. Dose reduction may be required for intolerance. In recent years, thiopurine metabolite testing to titrate dosage and allopurinol cotherapy was used to optimize thioguanine nucleotide levels.[19] Methotrexate was used primarily as a second-line therapy after failure of thiopurines, either orally or parenterally initiated at a dose of 25 mg per week with maintenance dosing of 15 mg per week. Third-line IMs were not analyzed as they account for a negligible case load. After initiation, IM were prescribed indefinitely unless ceased due to failure, side effects, complications, patient nonadherence, and/or other patient circumstances.

Statistical Analysis, Propensity Score Matching, and Ethics

Description of continuous variables was by median and interquartile ranges. Categorical variables were presented as percentages and analyzed by the chi-square test. Survival analysis was calculated using the log-rank score and data demonstrated using the Kaplan–Meier curve. Cox proportional hazards regression models (both univariate and multivariate) are expressed as hazard ratios (HR) with their 95% confidence intervals (CI).

Sensitivity analyses after strict propensity score matching was performed to control for possible confounders of treatment initiation for the first major surgery. The propensity score method is a tool to adjust a treatment effect for measured confounders.[24] The propensity scores for each patient was based on the covariates identified to predict the early use of IM and additional covariates known to be associated with requirement of surgery but not identified to be associated with early IM use. Using the propensity scores, early IM users were matched to patients with CD without early IM, using a 1- to 2-greedy matching algorithm, with a proximity caliper of 0.5. Similar matching was performed after excluding patients who had surgery within 6 months of diagnosis. Goodness of fit was evaluated by Hosmer–Lemeshow test, and the *P*-values were nonsignificant. Effect on early IM use on the time to surgery was assessed after propensity matching and expressed as HR with 95% CI. A *P*-value of <0.05 was considered statistically significant. Number needed to treat (NNT) to prevent a surgical event at 5 years from diagnosis and after initial surgery was based on the reported HR and survival at 5 years (SC5) in the control group ($NNR = 1/[SC5^{HR} - SC5]$).[25] Sample size target aimed to exceed similar published population-based cohorts that have recruited 310[7] to 506[6] CD cases with median follow-up for all time periods must be of at least 5 years. Statistical analysis was performed using IBM SPSS software version 20.0. The Sydney Local Health District Human Research Ethics Committee approved this study (HREC/10/CRGH/126).

RESULTS

Patient Characteristics

A total of 1035 consecutive patients with CD were recruited with median patient follow-up of 11.0 years (interquartile range, 5.0–19.0) and a collective follow-up of 13,061 patient-years. The patient characteristics at diagnosis are displayed in Table 1. Baseline characteristics at diagnosis remained similar across the decades of diagnosis apart from a nonsignificant trend toward increases in the prevalence of perianal and upper gastrointestinal disease locations (both $P = 0.07$).

Medical Interventions

The overall prevalence of 5-ASA, long-term corticosteroids, and anti-TNF therapy was 87.4%, 61.6%, and 12.2%, respectively (Table 2). Use of 5-ASA and long-term corticosteroids reduced significantly over time ($P < 0.0001$). A total of 437 patients (44.4%) were started on IM and of these, 384 patients (87.9%) continued treatment for 6 months or more, with a median duration of exposure of 2 years (range, 0–33) (Table 2). IMs used were thiopurines in 84.0% of cases and methotrexate in 14.9%, initiated after failure of thiopurines. Only 1.1% of patients with CD were initiated on methotrexate alone due to unfavorable thiopurine methyltransferase enzyme pharmacogenomics predictive of myelotoxicity and for concurrent treatment of inflammatory arthritic extraintestinal manifestation of CD. The median duration of disease at the time of IM commencement decreased from 26.5 years in Group A to 1.0 year in Group D ($P < 0.0001$). The probability of being maintained on IM at 1 and 5 years increased from 1.3% and 1.3% in Group A, 0.4% and 2.5% in Group B, 8.3% and 26.3% in group C, and 35.8% and 55.3% in Group D ($P < 0.0001$; Fig. 1).

On univariate analysis, the age of diagnosis phenotype A1 (age of onset ≤16 yr) and A2 (17–40 yr) predicted for early use of IM (HR, 2.98; 95% CI, 2.06–4.31; $P < 0.0001$ and HR, 1.77; 95% CI, 1.36–2.3; $P < 0.0001$, respectively). Other predictors of early IM use included: colonic disease location (HR, 0.77; 95% CI, 0.61–0.98), upper gastrointestinal disease location (HR, 2.76; 95% CI, 1.55–4.92; $P = 0.001$), perianal disease (HR, 1.66; 95% CI, 1.33–2.09; $P < 0.0001$), 5-ASA use (HR, 0.73; 95% CI, 0.55–0.96; $P = 0.026$), long-term corticosteroid use (HR, 1.5; 95% CI, 1.21–1.87; $P < 0.0001$), anti-TNF exposure (HR, 3.56; 95% CI, 2.84–4.55; $P < 0.0001$), and more recent time period of diagnosis (HR, 3.44; 95% CI, 2.93–4.04; $P < 0.0001$). On multivariate Cox proportional hazard regression analysis, the significant independent predictors of early IM use were young age of diagnosis below 16 years (HR, 2.44; 95% CI, 1.66–3.60) and 16 to 40 years (HR, 1.59; 95% CI, 1.21–2.09), long-term corticosteroid use (HR, 1.83; 95% CI, 1.45–2.31), anti-TNF exposure (HR, 1.82; 95% CI, 1.41–2.36), and the most recent decades of diagnosis (HR, 0.02–0.33, all $P < 0.0001$; Table 3).

Major Abdominal Surgery

A total of 388 (37.5%) had at least 1 major abdominal surgery, with 18.8% of these occurring within 6 months of diagnosis. Of those who had at least 1 recurrent operation, 117 (30.2%) underwent 2 or more major abdominal surgeries. A total of 9.2% of patients underwent perianal surgery, with 28.4% of these requiring repeat procedures. The types of surgical procedures performed remained similar across all study decades (Table 4). The risks of major abdominal surgery at 1, 5, and 10 years after diagnosis were 17.5%, 28.4%, and 39.5%. The risks of recurrent surgery at 1, 5, and 10 years after the first surgery were 5.9%, 19.0%, and 33.3%, respectively.

Factors Associated with the First Major Abdominal Surgery

All baseline characteristics at diagnosis and medication use were considered for the univariate analyses. Early IM use ($P < 0.0001$), long-term corticosteroid use ($P = 0.001$), 5-ASA use ($P < 0.0001$), age of diagnosis ($P < 0.0001$), location phenotype

TABLE 1. Clinical Characteristics at Diagnosis Grouped According to the Decade of Diagnosis

	Total (1970–2009)	Group A (1970–1979)	Group B (1980–1989)	Group C (1990–1999)	Group D (2000–2009)	*P*
No. of patients	1035	90	286	276	383	
Median follow-up (interquartile range), yr	11 (5–19)	29 (18–35.5)	20 (9–25)	14 (11–18)	5 (2–7)	<0.0001
Patient-years of follow-up	13,061	2400	4955	3712	1994	
Gender, N (%)						0.21
Men	450 (43.5)	31 (34.4)	119 (41.6)	125 (45.3)	175 (45.7)	
Women	585 (56.5)	59 (65.6)	167 (58.4)	151 (54.7)	208 (54.3)	
Median age at diagnosis (range), yr	29 (5–92)	28 (8–72)	28 (6–92)	30 (5–84)	30 (6–87)	0.28
Age, N (%)						0.16
Less than 16 yr (A1)	76 (7.3)	5 (5.6)	21 (7.3)	16 (5.8)	34 (8.9)	
Between 17 and 40 yr (A2)	653 (63.1)	68 (75.6)	179 (62.6)	171 (62.0)	235 (61.4)	
Age more than 40 yr (A3)	306 (29.6)	17 (18.9)	86 (30.1)	89 (32.2)	114 (29.8)	
Disease location, N (%)						0.52
Ileal (L1)	247 (24.0)	23 (25.6)	63 (22.1)	63 (23.1)	98 (25.8)	
Colonic (L2)	388 (37.7)	23 (25.6)	109 (38.2)	112 (41.0)	144 (37.9)	
Ileocolonic (L3)	393 (38.2)	44 (48.9)	113 (39.6)	98 (35.9)	138 (36.3)	
Not documented	7					
Gastroduodenal (L4)	17 (1.7)	0	1 (0.4)	6 (2.2)	10 (2.6)	0.07
Not documented	11					
Disease behavior, N (%)						0.52
Nonstricturing/nonpenetrating (B1)	697 (68.5)	52 (65.8)	186 (66.4)	196 (71.0)	263 (68.7)	
Stricturing (B2)	224 (22.0)	22 (27.8)	69 (24.6)	53 (19.2)	80 (20.9)	
Penetrating (B3)	97 (9.5)	5 (6.3)	25 (8.9)	27 (9.8)	40 (10.4)	
Not documented	17					
Perianal disease, N (%)						0.07
Yes	191 (18.5)	9 (10.3)	46 (16.1)	55 (19.9)	81 (21.1)	
No	840 (81.5)	78 (89.7)	239 (83.9)	221 (80.1)	302 (78.9)	
Not documented	4					
Extraintestinal manifestations, N (%)						0.10
Yes	191 (18.6)	16 (18.6)	60 (21.2)	38 (13.8)	77 (20.2)	
No	836 (81.4)	70 (81.4)	223 (78.8)	238 (86.2)	305 (79.8)	
Not documented	8					
Smoking status, N (%)						0.51
Current smokers	118 (20.1)	2 (11.1)	16 (26.2)	38 (20.5)	62 (19.2)	
Ex-smokers	140 (23.9)	7 (38.9)	15 (24.6)	46 (24.9)	72 (22.3)	
Nonsmokers	329 (56.0)	9 (50.0)	30 (49.2)	101 (54.6)	189 (58.5)	
Not documented	448					

TABLE 2. Drug Therapy During Follow-up Grouped According to Decade of Diagnosis (N [%] Within Time Period)

	Total (1970–2009)	Group A (1970–1979)	Group B (1980–1989)	Group C (1990–1999)	Group D (2000–2009)	*P*
Long-term corticosteroid	590 (59.2)	67 (77.0)	200 (72.5)	149 (58.0)	174 (46.2)	<0.0001
5-ASA	884 (86.3)	81 (95.3)	263 (93.6)	247 (89.8)	293 (76.5)	<0.0001
Anti-TNF	110 (10.6)	2 (2.2)	9 (3.1)	34 (12.4)	65 (17.0)	<0.0001
IMs	384 (39.0)	9 (12.0)	45 (18.0)	122 (44.2)	208 (54.3)	<0.0001
IMs within the first year of diagnosis	163 (16.6)	1 (1.3)	2 (0.8)	23 (8.3)	137 (35.8)	<0.0001
Early use of IMs	189 (19.2)	0	3 (1.2)	45 (16.3)	141 (36.8)	<0.0001
Exposed IM						0.957
Thiopurine	367 (84.0)	8 (80.0)	43 (82.7)	118 (83.1)	198 (85.0)	
Methotrexate	5 (1.1)	0	0	2 (1.4)	3 (1.3)	
Both	65 (14.9)	2 (20.0)	9 (17.3)	22 (15.5)	32 (13.7)	
Median time to starting IMs, yr	2	26.5	14	4.5	1	<0.0001

($P < 0.0001$), behavioral phenotype ($P < 0.0001$), and decade of diagnosis ($P = 0.002$) were each significantly associated with time to major abdominal surgery (see Table, Supplemental Digital Content 1, http://links.lww.com/IBD/A515). Anti-TNF use, gender, smoking, perianal involvement, upper gastrointestinal disease location, and extraintestinal manifestations at diagnosis were not associated with time to the first major abdominal surgery.

On multivariate analysis, early IM use was associated with decreased need for the first major abdominal surgery (HR, 0.45; 95% CI, 0.32–0.63; $P < 0.0001$) (Table 5). Colonic disease location (HR, 0.36; 95% CI, 0.27–0.50; $P < 0.0001$) and 5-ASA use (HR, 0.56; 95% CI, 0.41–0.76; $P < 0.0001$) were also associated with decreased need for surgery. Stricturing disease behavior (HR, 2.48; 95% CI; 1.93–3.20; $P < 0.0001$), penetrating disease behavior (HR, 2.97; 95% CI, 2.14–4.11; $P < 0.001$), and long-term corticosteroid use (HR, 1.41; 95% CI, 1.12–1.78; $P = 0.004$) were associated with increased need for the first major abdominal surgery. Neither the decade of diagnosis nor the age at diagnosis was significant independent predictors of surgery. The NNT with IM to prevent a surgical event at 5 years was 6.99 (95% CI, 5.34–11.95).

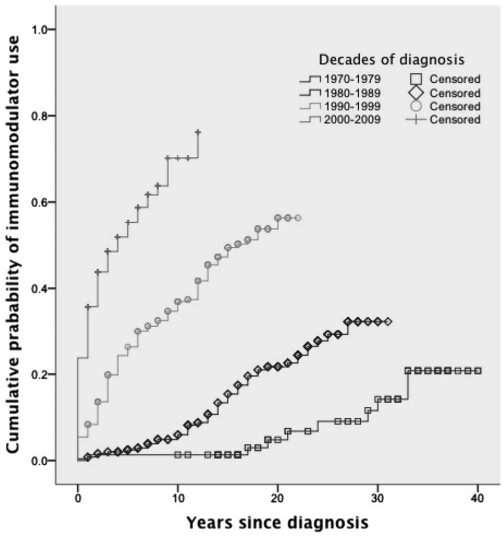

FIGURE 1. IM use according to the decade of diagnosis in patients with CD ($P < 0.0001$).

TABLE 3. Factors Affecting Time to Initiation of IM Therapy in CD on Cox Proportional Hazard Regression

	P	HR	95% CI
Age of diagnosis, yr	<0.0001		
<16	<0.0001	2.44	1.66–3.60
16–40	<0.001	1.59	1.21–2.09
>40	Reference		
Location at diagnosis	0.084		
Ileal	0.72	1.05	0.81–1.37
Colonic	0.062	0.79	0.62–1.01
Ileocolonic	Reference		
Perianal involvement	0.017	1.33	1.05–1.68
Long-term corticosteroid use	<0.0001	1.83	1.45–2.31
Anti-TNF exposure	<0.0001	1.82	1.41–2.36
Decade of diagnosis	<0.0001		
1970–1979	<0.0001	0.02	0.01–0.06
1980–1989	<0.0001	0.07	0.05–0.11
1990–1999	<0.0001	0.33	0.25–0.43
2000–2009	Reference		

Removed from the model: 5-ASA use ($P = 0.75$) and upper gastrointestinal disease location ($P = 0.39$).

TABLE 4. Types of First Major Abdominal Surgery Performed for CD at Anytime During Follow-up

Procedure Type	N (%)
Ileocecal resection/right hemicolectomy with ileal resection	219 (56.4)
Segmental resection of small bowel	67 (17.3)
Subtotal colectomy and colostomy	7 (1.8)
Total/subtotal colectomy and ileostomy	47 (12.1)
Loop ileostomy/colostomy	11 (2.8)
Subtotal colectomy and ileorectal anastomosis	30 (7.7)
Strictureplasty	3 (0.8)
Total colectomy and pouch formation	2 (0.5)
Abdominal exploration/abscess drainage	2 (0.5)

Propensity Score Matching and Sensitivity Analysis

A propensity score model was developed to quantify early IM use, using the factors predictive of early IM use and additional factors identified to affect surgical outcome. A total of 173 (96%) early IM users were matched against 266 controls who did not receive early IM. The mean propensity score of treated and controls were 0.42 and 0.15 before matching and 0.41 and 0.35 after matching. After matching, the relative multivariate imbalance improved from 0.73 to 0.58. Further matching was performed after excluding patients who had major abdominal surgery within 6 months of diagnosis, as IM therapy during this time may not have had sufficient time to reach peak efficacy to prevent surgery. A total of 165 (89%) of early IM users were matched against 251 controls. The relative multivariate imbalance improved from 0.66 to 0.43 after matching. In the propensity-matched analysis, early IM use was significantly associated with the requirement for the first major abdominal surgery in the overall cohort (HR, 0.54; 95% CI, 0.37–0.79; $P = 0.002$) (Fig. 2A) and also after excluding patients who had surgery within 6 months of their diagnosis (HR, 0.64; 95% CI, 0.42–0.96; $P = 0.034$).

Factors Associated with Recurrent Major Abdominal Surgery

All baseline characteristics at diagnosis and medication use were considered for the analysis. On univariate analysis, early IM use after the first major abdominal surgery ($P = 0.014$; Fig. 2B), anti-TNF use ($P = 0.024$), and long-term corticosteroid use ($P = 0.024$) were all associated with time to recurrent surgery. Decade of diagnosis was not associated with time to recurrent surgery ($P = 0.375$). On multivariate analysis, early IM use after the first surgery predicted reduced need for recurrent surgery (HR, 0.44; 95% CI, 0.25–0.79; $P = 0.006$). Anti-TNF use, however, was associated with an increased risk of recurrent surgery (HR, 1.7; 95% CI, 1.01–2.87, $P = 0.047$).

TABLE 5. Factors Affecting Time to Time to First Major Abdominal Surgery in CD on Multivariate Cox Proportional Hazard Regression

	P	HR	95% CI
Early IM use	<0.0001	0.45	0.32–0.63
Long-term steroid use	0.004	1.41	1.12–1.78
5-ASA use	<0.0001	0.56	0.41–0.76
Location at diagnosis	<0.0001		
Ileal	0.244	1.16	0.91–1.48
Colonic	<0.0001	0.36	0.27–0.50
Ileocolonic	Reference		
Behavior at diagnosis	<0.0001		
Inflammatory	Reference		
Stricturing	<0.0001	2.48	1.93–3.20
Penetrating	<0.0001	2.97	2.14–4.11

Removed from the model: age at diagnosis ($P = 0.239$), decade of diagnosis ($P = 0.309$).

The NNT with IM postsurgery to prevent reoperation at 5 years was 8.59 (95% CI, 6.26–23.93).

Factors Associated with Perianal Surgery

On univariate analysis, early IM was associated with the reduced need for perianal surgery ($P = 0.008$; Fig. 2C). On multivariate analysis, early IM use remained an independent predictor of reduced need for perianal surgery (HR, 0.30; 95% CI, 0.16–0.56; $P < 0.0001$). Anti-TNF use (HR, 1.73; 95% CI, 1.06–2.83; $P = 0.029$), long-term steroid use (HR, 1.71; 95% CI, 1.03–2.83; $P = 0.038$), and most recent decade of diagnosis (HR, 3.18; 95% CI, 1.59–6.33; $P = 0.001$) were associated with increased need for perianal surgery.

DISCUSSION

In this Australian specialist-based cohort study with sufficient sample size and duration of follow-up, significant reduction in the risk of initial and recurrent major abdominal surgery for CD were observed with the use of early IM therapy. Importantly, rather than simply being associated with treatment paradigm changes in recent decades, the reduction in surgery was independently and significantly associated with the early introduction of IM therapy within 3 years of diagnosis and maintained for at least 6 months. IM therapy was also defined by prescription of at least 6 months before the first major surgery to avoid biases of late and futile introduction of the drug.[10] Even adjusting for possible biases through rigorous analysis with propensity score matching and exclusion of subjects who required surgery within 6 months of diagnosis, significant reductions in both initial and recurrent surgery were observed. These findings support a possible change in the natural history of CD resulting from early and sustained IM early after diagnosis and after surgical intervention

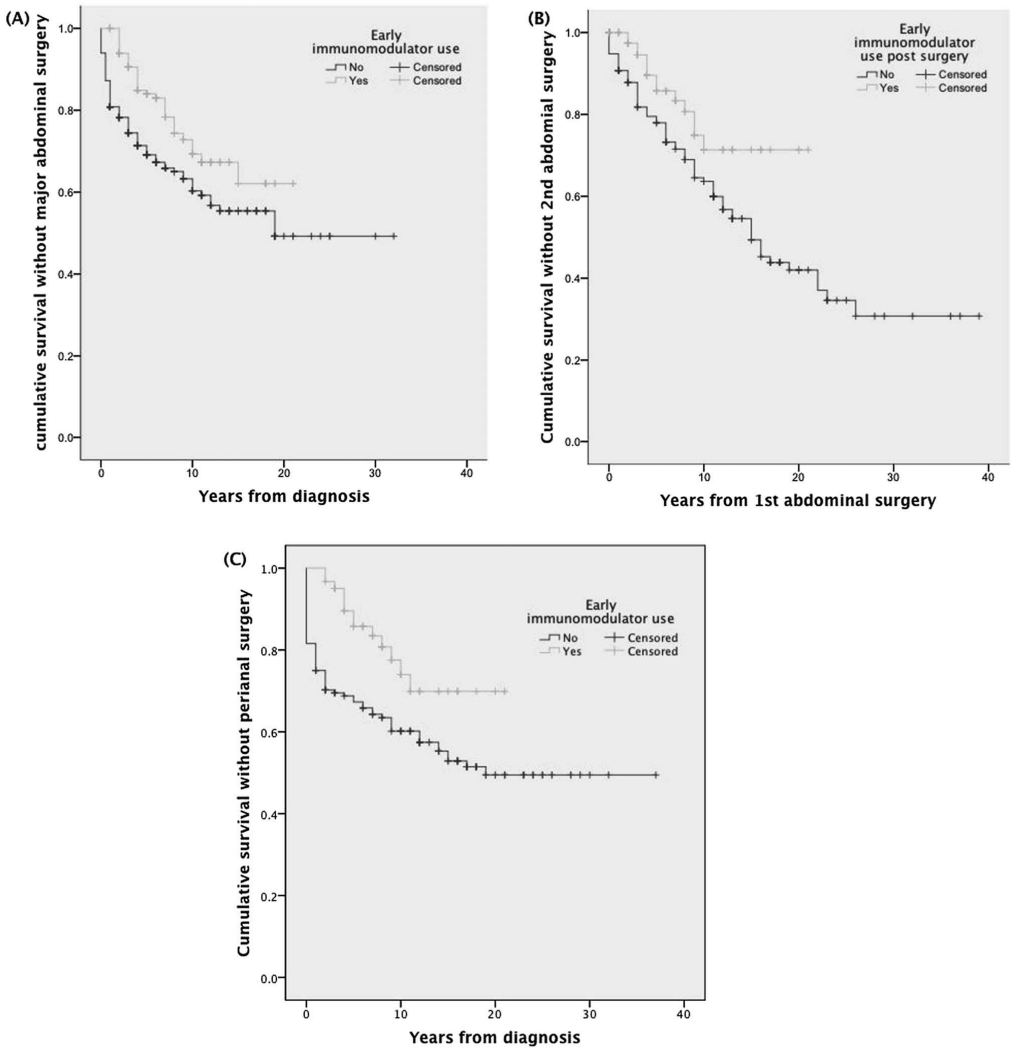

FIGURE 2. A, Association between early IM use and major abdominal surgery after propensity matching ($P = 0.001_{\text{Log-rank}}$). B, Association between early IM use and second major abdominal surgery ($P = 0.014_{\text{log-rank}}$). C, Association between early IM use and perianal surgery ($P = 0.008_{\text{log-rank}}$).

and were independent to the decade of diagnosis. Early IM therapy was also identified as the most significant independent predictor of the need for perianal surgery.

In Australia, the limitations on the use of anti-TNF agents have led to the increased reliance on and earlier introduction of IM. Although IM comprised almost universally of thiopurines as first-line agent, poor response, intolerance, hypersensitivity, idiosyncratic, and dose-related adverse reactions required the introduction of methotrexate as part of the IM strategy. This may increase the capture of subjects who benefit from early IM therapy, and the strategy might have been responsible for the reduction in major abdominal surgery in CD.

In the pediatric CD population, early introduction of azathioprine decreased the need for surgery.[24] However, in an adult population study from France, no reduction in the surgical resection rate was found despite an increase in the use of

azathioprine over time.[10,26] The latter study has been criticized by commencing IM too late in the disease course hence unable to modify disease natural history. A population-based study from Cardiff identified a significant reduction in surgical rates among patients diagnosed with CD between 1986 and 2003 that was independently associated with early introduction of azathioprine.[2] However, the year of diagnosis was an independent predictor of surgery indicating that changes in surgical treatment paradigms over time may have been responsible for the reduction in surgical rates. The protective effect of IM was also demonstrated by Lakatos et al,[6] a recently published study from western Hungary, in which early commencement of azathioprine was found to reduce the need for the first surgery independent to the decade of diagnosis. Strict definitions for early IM use and propensity score matching to eliminate bias in their study design were applied, as was the case in this study, and correcting for biases may differentiate our results from the previously published negative studies.

The benefit of thiopurines in preventing postoperative recurrence has been demonstrated in clinical trial settings.[27,28] However, population-based studies have yet to confirm this benefit.[7] A recent retrospective analysis demonstrated a significant reduction in postoperative recurrence associated with azathioprine exposure for at least 36 months, initiated between 3 and 60 months after the initial surgery.[29] The study could be criticized by not addressing the immortality bias favoring azathioprine. To correct for this bias in studying whether IM can reduce the need for recurrent surgery, we only included IM use within 3 years of the index major abdominal surgery that was maintained for at least 6 months. Using these strict definitions, we have demonstrated the benefit of early IM use in preventing surgical recurrence.

The increased risk of recurrent surgery and perianal surgery associated with use of anti-TNF therapy must be interpreted with caution, given its use at the time of patient recruitment was before their regulatory approval for reimbursement. Anti-TNF treatments were given on an episodic basis and reserved for complicated and severe disease late in the disease course. Since that time, biological therapies have been given in accordance to the best practice as scheduled maintenance and earlier in the course of disease.[30] Even with scheduled maintenance biological agents, they may be associated with high cost, risk of severe adverse reactions including life-threatening infections, primary nonresponse in one-third of patients and progressive secondary loss of response.[30 32] As such, effective, cheaper, and easy-to-administer IM medications that can be prescribed with a high-level of confidence by physicians are required.[33]

There are a few limitations of this study. The study population was an ambulatory nonhospital-based specialist-referred cohort, based within the Sydney Local Health District rather from national databases. However, recruitment of ambulatory patients managed continuously by gastroenterologists with excellent longitudinal follow-up and documentation allowed for excellent characterization of every case and ensured the definition of IM was met. Similar strategies have been employed in other Australian and New Zealand population-based cohort.[17,34] Reassuringly, the 1-, 5-, and 10-year risk of the first surgery in the current cohort are similar to the pooled 1-, 5-, and 10-year risk of surgery published from a meta-analysis of population-based studies.[35] The recruitment strategy also provided sufficient patient-years of follow-up required to not only demonstrate initial surgical rates within 5 years of diagnosis, but also recurrent surgical rates that few studies have published to date. Scrutiny of individual cases is often not possible using larger population cohorts and misclassification may confound results. Second, patient management strategies and diagnostic tests have changed over time and may have accounted for changes in surgical rates. This, however, was corrected for by including "decade of diagnosis" as a variable in the multivariate analysis, which failed to be an independent predictive variable for surgery. Early IM use was the only controllable factor that significantly decreased initial and recurrent major abdominal surgery in CD. Thirdly, this was not a randomized placebo-controlled study. However, such studies may be limited with their patient-years of follow-up in identifying surgical events and the need for recurrent surgeries. In their control groups, high proportions of controls eventually required commencement of thiopurines.[11,12] Such studies may require per protocol analysis, very large sample sizes studied over many years to identify the true benefits of thiopurines. These studies also did not take into account the possible benefit of second-line methotrexate after the high dropout rates that occur with thiopurine treatment. This study ensured the robustness of the diagnosis, conformity of evidence-based management, and case definitions that may be lacking in studies derived from insurance data, hospital coding, or deidentified data that cannot be verified. Finally, this study was not designed to be analyzed according to intention to treat. The duration of IM use criteria had to be met on a per protocol basis to test the absolute benefit of early IM therapy over time. Reasons for ceasing IM therapy, although not specifically reported here, were similar to those previously published.[13]

The strengths of this study included the large size of the cohort, the long duration of follow-up, and the completeness of disease characterization from the initial point of contact. Rigorous monitoring and validation of data capture were possible. This is the first study that included methotrexate use for those who had failed thiopurines to test the real-life option of the IM strategy. The IM strategy has been well verified in this and other studies to have steroid-sparing effects but this study adds to the few that demonstrate significant reduction in both initial and recurrent surgery associated with their earlier initiation and sustained use. This study is also one of only a few to use propensity score matching to correct for biases, which may reduce type II errors and also to calculate the NNT to prevent a surgical event. Given their low cost in comparison with biological agents and expensive and disabling surgical event, IM therapy needs to be advocated to remain within the armamentarium for the treatment of IBD.[33] Data to demonstrate absolute improved outcomes, however, are also needed to support their use given their known risk of adverse

events. These data support the earlier introduction of thiopurines and methotrexate for those that fail thiopurines in CD.

In conclusion, early and sustained use of IM after diagnosis and after surgery was significantly associated with a reduction in the risk of abdominal and perianal surgery in CD. The results on abdominal surgery are independent to decade of diagnosis suggesting a true drug-induced beneficial effect in improving long-term outcomes, and support their ongoing use in the treatment of CD.

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APPENDIX 2 – STUDY 3 – PUBLISHED ARTCLE

ORIGINAL ARTICLE

Thiopurines Dosed to a Therapeutic 6-Thioguanine Level in Combination with Adalimumab Are More Effective Than Subtherapeutic Thiopurine-based Combination Therapy or Adalimumab Monotherapy During Induction and Maintenance in Patients with Long-standing Crohn's Disease

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Background: The benefit of concomitant immunomodulation with adalimumab (ADA) in Crohn's disease is poorly understood. We aimed to compare ADA monotherapy with combination therapy with thiopurines, stratified by thioguanine nucleotides (TGNs).

Methods: Retrospective observational study of ADA induction and maintenance. Thiopurines were classified according to TGNs (>235 pmol/8 × 10^8 red blood cell therapeutic).

Results: At induction, response was more frequent in combination than ADA monotherapy (83% versus 61%, $P = 0.02$) and with therapeutic compared with subtherapeutic TGNs (87% versus 70% $P = 0.011$). Among 280 maintenance semesters in 91 patients, remission was higher with combination than monotherapy (81% versus 60%, $P < 0.0001$) and therapeutic versus subtherapeutic TGNs (85% versus 58%, $P = 0.004$). Therapeutic TGN (odds ratio [OR] 4.32, 95% CI, 1.41–13.29, $P = 0.01$) and albumin (OR 1.09, 95% CI, 1.01–1.18, $P = 0.03$) were predictors of response to induction. Therapeutic TGN (OR 3.71, 95% CI, 1.87–7.34, $P < 0.0001$) and ileal disease (OR 0.21, 95% CI, 0.08–0.57, $P = 0.002$) were predictors of remission semesters. Concomitant immunomodulation at induction was associated with longer time to failure (69 versus 36 months, $P = 0.009$). Therapeutic TGN at induction ($P = 0.03$) and male sex ($P = 0.026$) were associated with time to failure.

Conclusions: Combination therapy was superior to ADA monotherapy for induction and during maintenance. This benefit was increased further when thiopurines resulted in therapeutic TGNs. Early use of adequately dosed thiopurines (≥3 months before starting ADA) was associated with improved clinical outcomes.

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Key Words: Crohn's disease, thiopurine, combination therapy, adalimumab

Adalimumab (ADA, Humira; Abbott Laboratories, Abbott Park, IL), a fully humanized monoclonal IgG antibody directed against tumor necrosis factor (TNF) alpha, is effective at inducing and maintaining remission in patients with moderate-to-severe Crohn's disease.[1–5] However, a proportion of patients fail to respond to ADA. Of those who do respond, approximately

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30% lose response by 12 months, with a further 10% losing response annually thereafter.[5–7] Accordingly, there is a need to understand whether there are factors that are associated with response and loss of response to improve outcomes.

Immunogenicity is a well-recognized mechanism implicated in ADA failure.[8] Antibodies to ADA have been shown to influence the pharmacokinetics of ADA, leading to increased drug clearance and lower ADA levels.[9] The use of concomitant immunomodulation (CIM) with anti-TNF agents decreases antidrug antibody formation.[10–12] In the case of infliximab (IFX), combination therapy is superior to monotherapy both for patients with Crohn's disease and those with ulcerative colitis.[11–13] However, there is less evidence for a similar effect with ADA. A recently published prospective open-label study of 176 treatment-naive patients with moderate-to-severe Crohn's disease randomized to ADA monotherapy compared with combination therapy with azathioprine (AZA) found no difference in rates of clinical remission at week 26.[14] Furthermore, there were no differences in the proportion of patients meeting the primary endpoint when patients were stratified according to week 12 thioguanine nucleotide (TGN) threshold of 250 pmol/8 $\times$ 10^8 red blood cell (RBC) ($P = 0.13$). However, they found significantly higher endoscopic remission at week 26 in the combination group, indicating likely benefit of combination therapy. Further evidence regarding the need for CIM when using ADA is based on subanalysis of randomized controlled trials and retrospective studies.[8,15] The results of these studies are conflicting, suggesting that further data would be of use. Studies assessing whether the intensity of CIM (in the case of thiopurines measured using 6-thioguanine nucleotide metabolites [TGN]) is of importance are lacking, an area recently addressed in 2 IFX-treated cohorts.[16,17]

The aim of this study was, therefore, to investigate the influence of CIM on clinical outcomes in a well-characterized and prospectively assessed cohort of Crohn's disease patients treated with ADA. In addition, we aimed to assess whether therapeutic TGN concentrations were associated with improved outcomes compared with subtherapeutic TGNs in patients on thiopurine combination therapy.

METHODS

Study Design

We performed a retrospective single-center cohort study of consecutive patients with moderate-to-severe Crohn's disease, who commenced ADA at Guy's and St. Thomas' Inflammatory Bowel Disease Centre between January 2006 and June 2013.

Study Population

The diagnosis of Crohn's disease was based on standard endoscopic, histological, and radiological criteria.[18] Only patients who commenced ADA at our center were included. Data were collected prospectively from January 2009 through our Virtual Biologic Clinic which has been described previously.[19] Within this setting, patients are reviewed before commencing ADA and subsequently every 3 to 6 months, unless indicated earlier. All other data were retrieved from the electronic patient record.

Thiopurines (AZA, mercaptopurine, and thioguanine) or methotrexate (MTX) was commenced at the treating physician's discretion. AZA and mercaptopurine were initially dosed according to body weight (2–2.5 mg/kg AZA, 1–1.5 mg/kg mercaptopurine) after measurement of thiopurine-S-methyltransferase activity[20–22] with dose reduction by 50% in thiopurine-S-methyltransferase heterozygotes.[23] We routinely measure thiopurine metabolites in all patients (TGN and methylated metabolites)[24] 4 weeks after starting therapy to guide dose adjustment; a TGN of 230 to 450 pmol/8 $\times$ 10^8 RBC is considered therapeutic.[25] Patients with subtherapeutic TGNs, evidence of hepatotoxicity or intolerance in conjunction with a metabolite profile consistent with hypermethylation (defined as methylated metabolites to TGN ratio $>$ 11:1), were changed to allopurinol 100 mg coprescription with thiopurine dose reduction to 25% to 33% of the original dose.[26] During maintenance, TGNs are routinely performed in patients every 6 to 12 months. MTX was dosed at 15 to 25 mg weekly orally with folic acid supplementation[27] and thioguanine at 20 to 40 mg daily.

Biologics were started as a step-up therapy in patients who either failed or intolerant of immunomodulators. ADA was initiated as the first-line biologic or after failure of IFX. All patients initiated ADA at standard induction dosing (160/80 mg weeks 0 and 2), followed by maintenance (40 mg every other week). In those with an incomplete response after induction or secondary loss of response, ADA was intensified to 40 mg each week. Dose reduction back to 40 mg every other week was considered after attainment of remission, based on a combination of clinical, biochemical, endoscopic, and radiological parameters.

Assessment of Response—Induction

Response to induction was assessed at 12 weeks by physician global assessment after consideration of clinical activity (Harvey–Bradshaw Index[28] [HBI]), biomarkers (C-reactive protein, [CRP], fecal calprotectin), and imaging or endoscopy, where available. HBI of $<$4, CRP $<$ 5 mg/L, and calprotectin $<$50 mg/g were considered as markers of response. Patient response was assessed and documented by at least 2 or more experienced inflammatory bowel disease physicians after considering all available parameters.

Patients maintained on a stable dose of immunomodulator $\geq$3 months before ADA induction and who continued for a $\geq$6 months after induction were defined as CIM at induction. All other patients were classified as not being on CIM at induction. Patients taking thiopurines were further classified according to TGN levels; $>$ 235 was considered therapeutic.

Assessment of Response—Maintenance

Beginning after the first 12 months of treatment, patients were assessed for long-term clinical response, per 6-monthly semesters. Semesters with $\geq$3 months of CIM therapy were considered CIM semesters. Patients on thiopurines were again stratified according to TGNs measured from each semester, where available. Semesters were classified per one of 3 definitions:

Flare semester: active clinical disease resulting in treatment intensification (ADA dose escalation, new corticosteroids, or addition of CIM), hospital admission due to active Crohn's disease, new perianal disease or Crohn's disease-related surgery not leading to ADA withdrawal.

Remission semester: semester without a flare either on every other week or weekly dosing.

Failure semester: Failure, defined as withdrawal of ADA due to primary nonresponse, secondary loss of response despite dose intensification, or due to development of adverse effects or complications.

Factors Associated with Clinical Response

Covariates that were assessed for response to induction, ADA failure, dose intensification, and semester outcomes included sex, disease duration, age at diagnosis, disease location and behavior as per Montreal classification,[29] smoking status, weight, previous anti-TNF exposure, previous surgery, CIM ≥3 months before starting therapy, CIM status during semester, and CRP and HBI at commencing ADA. Interactions between weight and need for ADA dose intensification were also explored.

Statistical Analysis

Categorical variables are presented as number and percentage, and quantitative data as mean with standard deviation or median with interquartile range, as appropriate. Between-group comparisons were performed using Pearson's Chi-squared, independent sample *t* test, or Mann–Whitney U test. Multivariate analysis was performed using Cox regression for time to failure and binary logistic regression for factors associated with induction outcome, dose escalation, and semesters of remission. Covariates identified a priori with $P < 0.1$ on univariate analysis were entered into a multivariate backward stepwise model. Variables with $P < 0.05$ were retained in the final model and reported as adjusted hazard ratios (HRs) in the Cox regression and odds ratios (ORs) in logistic regression with 95% confidence intervals (CIs). Time to ADA failure was calculated using Kaplan–Meir survival analysis, and comparisons between groups were made using the log-rank test. Two-sided *P* values <0.05 were considered significant. Statistical analyses were carried out using SPSS v23.0 (SPSS Inc., Chicago, IL).

Ethical Consideration

According to the guidelines of the U.K. Health Research Authority, as the data collected were done so as part of routine clinical care and were evaluated retrospectively, ethical approval was not required.[30]

RESULTS

Patient Characteristics

One hundred fifty-six patients commenced ADA between January 2006 and June 2013; 123 met inclusion criteria for the induction analysis (Fig. 1). Patient characteristics are shown in Table 1. CIM was prescribed for ≥3 months before starting ADA in 77/123 (63%); thiopurines were used in 67/77, MTX in 6, thioguanine in 3, and mycophenolate mofetil in 1. Fifty-seven percent and 59% of patients had previously been exposed to anti-TNF in the CIM and no-CIM cohorts, respectively. No significant differences in baseline CRP, ($P = 0.49$), albumin ($P = 0.19$), or HBI ($P = 0.052$) were observed between CIM and no-CIM groups. Follow-up was similar in both groups (20 versus 22 months, $P = 0.4$).

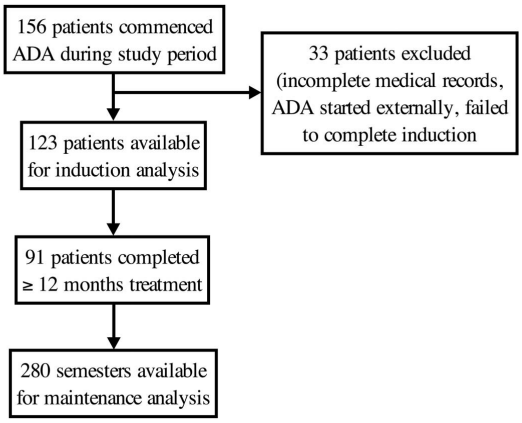

FIGURE 1. Flow diagram of patient recruitment.

A total of 280 semesters among 91 patients were available for the maintenance analysis; 201 (72%) were classified as CIM semesters (143 with immunomodulators ≥3 months before starting ADA versus 58 who were not) compared with 79 (28%) ADA monotherapy semesters (20 in patients treated with immunomodulators ≥3 months before starting ADA versus 59 who were not) ($P < 0.001$). Thiopurines were used in 84% of semesters, of these TGNs were available in 92%; 135 (88%) were therapeutic and 19 (12%) were subtherapeutic.

Primary Response

Complete response was seen in 92/123 (75%) at week 12; the mean CRP improved from 18.8 to 4.4 mg/L and the HBI from 7.5 to 1.6 (see Table, Supplemental Digital Content 1a, http://links.lww.com/IBD/B547). Among complete responders' clinical remission with HBI ≤4 was seen among 92% and biochemical remission with CRP normalization (<5 mg/L) in 84%. A total of 76.5% achieved both clinical and biochemical remission (see Table, Supplemental Digital Content 1b, http://links.lww.com/IBD/B547). The rate of primary nonresponse was significantly lower among patients treated with CIM (12% versus 30%, $P = 0.02$) (Fig. 2). In addition, complete response was also higher among those treated with CIM compared with those not treated with CIM (83% versus 61%, $P = 0.02$).

Most (97%) patients treated with thiopurines had TGNs measured before starting ADA; 16% were subtherapeutic. Response to induction was seen in 48 (87%), 7 (70%), and 28 (61%) of those with therapeutic TGNs, subtherapeutic TGNs, and no-CIM, respectively ($P = 0.011$) (Fig. 3).

TABLE 1. Baseline Characteristics at Adalimumab (ADA) Initiation (n = 123)

Characteristics	CIM (n = 77)	No-CIM (n = 46)	*P*
Male, n (%)	40 (51.9)	25 (54.3)	0.79
Age at diagnosis, median (IQR)	21 (17–28)	22 (18–29)	0.32
Disease duration years, median (IQR)	11 (4.5–16)	9 (3.5–17.2)	0.46
Location L1:L2:L3 (%)	15.6:19.5:64.9	10.9:28.3:60.9	0.46
Upper GI involvement (%)	16.9	19.6	0.71
Behavior B1:B2:B3 (%)	36.4:44.2:19.4	37.0:43.5:19.5	0.99
Perianal disease (%)	31.2	41.3	0.25
EIM (%)	19.7	21.7	0.79
Weight (kg), median (IQR)	66.0 (54.4–78.9)	69.5 (59.5–83.5)	0.35
Current smoker (%)	10.6	22.0	0.28
Family history (no:first deg:other) (%)	90.3:6.5:3.2	84.6:12.8:2.6	0.54
Previous surgery, n (%)	41 (53.2)	18 (39.1)	0.13
Perianal surgery, n (%)	13 (16.9)	7 (15.2)	0.81
Steroids at ADA induction (%)	19.5	41.3	0.01
5-ASA (%)	6.5	17.4	0.06
Previous anti-TNF exposure (%)	55.8	58.7	0.76
IFX/ADA/both (%)	50.0; 2.6; 3.9	45.7; 2.2; 10.9	0.52
CRP (mg/L), mean (SD)	20.7 (28.5)	25.1 (30.3)	0.49
Albumin (g/L), mean (SD)	42.3 (6.6)	42.0 (4.1)	0.20
HBI, mean (SD)	7.1 (4.4)	9.0 (4.5)	0.05

EIM, extraintestinal manifestation; IQR, interquartile range.

In univariate analysis, CIM use at induction and serum albumin were significantly associated with response at week 12 (Table 2). On multivariate analysis, therapeutic TGN levels (OR 4.32, 95% CI, 1.41–13.29, $P = 0.01$) and albumin level (OR 1.09, 95% CI, 1.01–1.18, $P = 0.03$) were independent predictors of response to induction (Table 2).

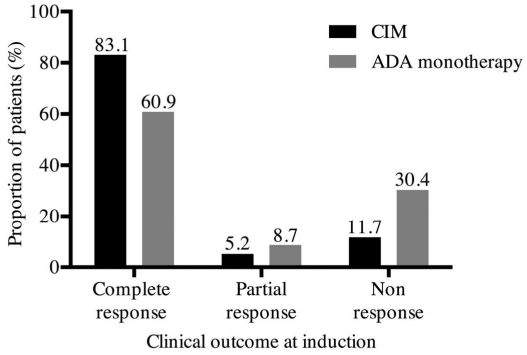

FIGURE 2. Clinical response after induction comparing concomitant immunomodulation to adalimumab monotherapy. Complete response to induction was observed more frequently in patients treated with ADA and CIM compared with ADA monotherapy (83.1% versus 60.9%, $P = 0.02$).

Semester Analysis

Of 280 semesters, every other week dosing was observed in 200 (72%) and weekly in 80 (29%). A similar proportion of CIM and non-CIM semesters were observed in each dosing regimen (every other week 74 versus weekly 68%, $P = 0.31$). More CIM

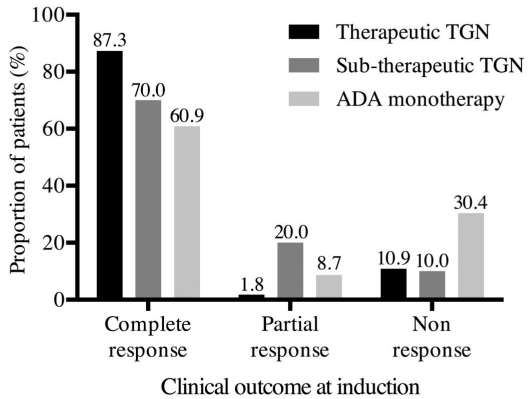

FIGURE 3. Clinical response after induction stratified by TGN and ADA monotherapy. Complete response was observed more frequently in patients with therapeutic TGN versus subtherapeutic TGN versus ADA monotherapy (87.3% versus 70.0% versus 60.9%, $P = 0.011$).

TABLE 2. Univariate and Multivariate Predictors of Response at Week 12

	Univariate		Multivariate	
Covariant	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex	0.51 (0.20–1.28)	0.15		
Age at diagnosis	1.02 (0.97–1.08)	0.46		
Disease duration at start of ADA	1.00 (0.95–1.05)	0.99		
Montreal location (reference L3)				
L1	0.65 (0.18–2.31)	0.51		
L2	0.73 (0.25–2.16)	0.57		
Montreal location L4	1.04 (0.32–3.43)	0.94		
Montreal behavior (reference B3)				
B1	1.22 (0.35–4.23)	0.76		
B2	1.16 (0.35–3.85)	0.81		
EIM	1.91 (0.52–7.00)	0.33		
Weight (kg)	1.02 (0.98–1.05)	0.31		
Current smoker	0.83 (0.45–1.54)	0.55		
Family history of IBD	1.39 (0.36–5.33)	0.63		
Previous bowel resection	1.01 (0.41–2.49)	0.98		
Exposure to anti-TNF	1.02 (0.41–2.54)	0.97		
Steroids at induction	0.66 (0.25–1.73)	0.39		
5-ASA at induction	0.74 (0.19–2.94)	0.67		
CIM (reference no-CIM)				
Subtherapeutic TGN	3.94 (0.45–34.12)	0.21	3.36 (0.38–29.79)	0.28
Therapeutic TGN	3.57 (1.24–10.26)	0.18	4.32 (1.41–13.29)	0.01
CRP at induction	0.99 (0.98–1.00)	0.09	Removed	0.35
Albumin at induction	1.08 (1.01–1.17)	0.03	1.09 (1.01–1.18)	0.03
HBI at induction	0.95 (0.86–1.05)	0.95		

5-ASA, 5-aminosalicylic acid; EIM, extraintestinal manifestation; IBD, inflammatory bowel disease.

semesters were classified as remission compared with non-CIM semesters (81% versus 60%, $P < 0.0001$, Fig. 3). Considering CIM semesters, patients with therapeutic TGNs were more likely to be in remission compared with those with subtherapeutic TGNs (86% versus 58%, $P = 0.004$) (Fig. 4).

In univariate analysis, ileal location ($P = 0.001$), extraintestinal manifestations of disease ($P = 0.03$), and semesters with therapeutic TGNs ($P < 0.0001$) were associated with remission (Table 3). These covariates remained significant after multivariate analysis (ileal disease location: OR 0.21, 95% CI, 0.08–0.57, $P = 0.002$, therapeutic TGN: OR 3.71, 95% CI, 1.87–7.34, $P < 0.0001$).

Factors Associated with ADA Failure

Thirty-five of 123 (29%) ceased ADA during the study; 5/35 withdrew because of sustained clinical remission. A further 2/35 prescribed ADA to downstage inflammation preoperatively were not continued postoperatively. Hence, 28 patients were subsequently analyzed with regard to ADA failure. The mean time to failure was 58 months (95% CI, 50.5–66.3). CIM ≥3 months before ADA was associated with longer time to failure compared with those not treated with CIM (68.5 versus 35.7 months, $P = 0.009_{\text{log rank}}$) (Fig. 5).

On univariate analysis, male sex ($P = 0.033$) and therapeutic TGN ($P = 0.03$) were associated with time to failure (Table 4). Therapeutic TGN ≥3 months before ADA (HR 0.37, 95% CI, 0.15–0.89, $P = 0.026$) and male sex (HR 0.39, 95% CI, 0.17–0.91, $P = 0.028$) were independently associated with time to failure on Cox regression analysis. Dose escalation did not predict subsequent ADA failure ($P = 0.20$). CIM ≥3 months before ADA was independently associated with time to failure (HR 0.37, 95% CI, 0.17–0.81, $P = 0.012$).

Dose Escalation and Factors Associated with Dose Escalation

ADA was escalated to weekly dosing in 34/123 (28%) patients. The mean time to dose escalation was 12.5 months (SD 8.7). All baseline characteristics were considered for univariate analysis (see Table, Supplemental Digital Content 2, http://links.lww.com/IBD/B548). On multivariate analysis CIM ≥3 months before starting ADA was not associated with time to dose escalation (HR 0.55, 95% CI, 0.28–1.09, $P = 0.088$). Baseline CRP

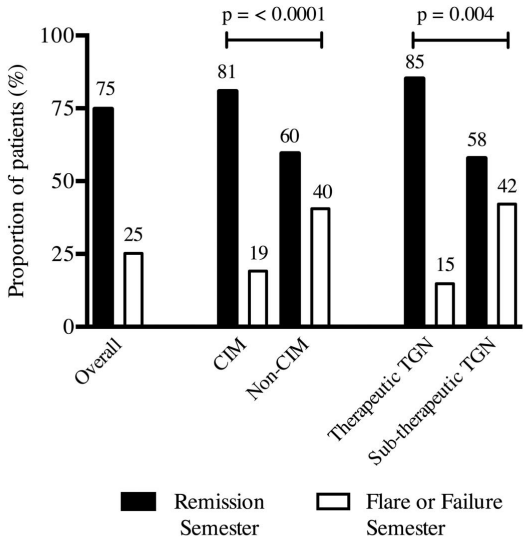

FIGURE 4. Association between semester outcomes overall and according to CIM and TGN status.

(HR 1.01, 95% CI, 1.001–1.024, $P = 0.035$) and 5-aminosalicylic acid treatment at ADA initiation (HR 3.97, 95% CI, 1.68–9.40, $P = 0.002$) were significant independent predictors associated with time to dose escalation on multivariate analysis.

Adverse Events

Serious adverse events occurred in 5 patients during the study. Two malignancies occurred; metastatic breast cancer after 19 months of combination treatment with thioguanine and ADA and transitional cell carcinoma of the bladder after 27 months of ADA monotherapy. A 25-year-old male treated with thioguanine and ADA developed primary EBV infection and recovered after discontinuing both drugs. Two patients developed intraabdominal sepsis, 4 and 10 months into treatment; one was on ADA monotherapy, and the other on combination therapy with AZA.

DISCUSSION

We have demonstrated that in patients with Crohn's disease starting ADA, combination therapy with an immunomodulator was associated with higher rates of clinical response after induction compared with ADA monotherapy and observed lower rates of subsequent ADA failure. During maintenance, combination therapy was associated with a decrease in the proportion of flare semesters. We assessed the relationship of thiopurines stratified according to TGN levels, not previously reported in the literature, and found that subtherapeutic TGNs at induction and during maintenance therapy were associated with worse clinical outcomes and an increased risk of ADA failure compared with patients with therapeutic TGNs.

The situation regarding combination therapy in patients taking IFX has been studied extensively. In a retrospective analysis of 584 semesters among 121 patients with inflammatory bowel disease, Sokol et al found a significantly decreased incidence of flares (32% versus 19%), perianal complications (12% versus 4%), and mean CRP (11% versus 9%) in those treated with combination therapy compared with IFX monotherapy.[31] Many of the patients in this cohort started IFX on failure of immunomodulator therapy and continued CIM after initiating IFX, suggesting that there is a benefit of combination therapy in all patients starting IFX, not just those naive to immunomodulators. This has also been supported by a recent meta-analyses of patient-level data in the biological registration trials.[32] In addition, combination therapy has been shown to improve rates of deep remission (defined as clinical remission together with normalization of CRP and mucosal healing), compared with IFX monotherapy in patients who were previously naive to both drugs (65% versus 25%, $P = 0.037$).[17]

Although the benefits of combination therapy with IFX seem robust, evidence to support the same benefit with ADA is relatively sparse. The same meta-analysis of randomized controlled trials demonstrating a benefit of combination therapy in induction of clinical remission at 6 months with IFX found no such association for combination therapy with ADA (OR 0.88, 95% CI, 0.58–1.35).[32] A recent prospective study randomizing treatment-naive patients with moderate-to-severe Crohn's disease to either ADA monotherapy or combination therapy with a thiopurine found no difference in clinical remission at week 26 between the 2 treatment arms (72% versus 68%) although an improvement in endoscopic activity at week 26 and higher ADA trough levels were observed in those treated with combination therapy.[14]

Conversely, a recent meta-analysis among patients with Crohn's disease found that ADA monotherapy was slightly inferior to combination therapy for induction of remission (OR 0.78, 95% CI, 0.64–0.96, $P = 0.02$) although no such benefit was seen for maintenance of clinical remission (OR 1.08, 95% CI, 0.79–1.48, $P = 0.48$) nor was combination therapy superior to monotherapy in terms of need for dose escalation (OR 1.13, 95% CI, 0.69–1.85, $P = 0.62$).[33]

Our study builds on previously published open data. A retrospective study from 2 large centers described 207 patients with Crohn's disease and found that CIM maintained for 3 months or more within 6 months of initiating ADA was associated with a lower risk of ADA failure and fewer flare semesters during maintenance.[15] CIM was not, however, associated with improved rates of response to induction therapy nor was ongoing CIM associated with fewer semesters of flare nor with a lower risk of ADA failure. Semesters in which ADA was dosed weekly, rather than every other week, were classified as flares, even if the patient remained well during the semester, which may have influenced these results. It is recognized that secondary loss of response

TABLE 3. Univariate and Multivariate Predictors of Remission Semesters

	Univariate		Multivariate	
Covariant	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex	1.69 (0.97–2.95)	0.06	1.77 (0.91–3.44)	0.09
Age at diagnosis	0.99 (0.97–1.02)	0.72		
Disease duration at start of ADA	1.03 (0.99–1.07)	0.09	Removed	0.26
Montreal location (reference L3)				
L1	0.25 (0.11–0.56)	0.001	0.21 (0.08–0.57)	0.002
L2	0.57 (0.29–1.09)	0.09	0.50 (0.24–1.04)	0.064
Montreal location L4	0.83 (0.43–1.59)	0.57		
Montreal behavior (reference B3)			Removed	
B1	0.54 (0.23–1.31)	0.17		0.49
B2	0.46 (0.20–1.07)	0.07		0.25
EIM	2.08 (1.07–4.07)	0.03	Removed	0.11
Weight, kg	1.00 (0.98–1.02)	0.87		
Current smoker	0.93 (0.63–1.36)	0.69		
Family history of IBD	0.97 (0.53–1.93)	0.97		
Previous bowel resection	0.91 (0.53–1.56)	0.73		
Previous perianal surgery	0.47 (0.24–0.91)	0.25	Removed	0.99
Exposure to anti-TNF	0.79 (0.44–1.42)	0.44		
Steroids at induction	0.76 (0.43–1.33)	0.33		
5-ASA at induction	0.50 (0.24–1.03)	0.06	Removed	0.15
CIM induction (reference no-CIM)				
Subtherapeutic TGN	0.71 (0.24–2.05)	0.52		
Therapeutic TGN	1.58 (0.83–3.02)	0.17		
Semester CIM (reference no-CIM)				
Subtherapeutic TGN	0.94 (0.34–2.58)	0.90	1.11 (0.37–3.26)	0.86
Therapeutic TGN	3.91 (2.04–7.53)	<0.0001	3.71 (1.87–7.34)	<0.0001
CRP at induction	0.56 (0.97–1.01)	0.56		
Albumin at induction	1.01 (0.86–1.06)	0.81		

5-ASA, 5-aminosalicylic acid; EIM, extraintestinal manifestation; IBD, inflammatory bowel disease.

occurs in a significant proportion of patients during ADA maintenance, and that dose escalation can recapture response in many.[6] It is possible to argue that patients who regain response on dose escalation and remain well on weekly dosing are, therefore, not treatment failures but, rather, represent a subgroup of patients who require higher dosing to achieve therapeutic drug levels to maintain remission.[34] In the current study, therefore, a semester requiring dose escalation was classified as a flare; subsequent semesters were classified according to clinical status and were not automatically recorded as flare semesters based on the need for weekly dosing. Interestingly, dose escalation was not associated with time to failure, supporting our study design.

For the first time, we report the association between adequate dosing of thiopurines (TGN > 235 pmol/8 × 10^8 RBC) and clinical response. We found significantly higher response rates in patients with therapeutic compared with subtherapeutic TGNs at both induction (88% versus 70%) and during maintenance (85% versus 58%). In this regard, data are beginning to emerge demonstrating that the intensity of CIM influences the pharmacokinetics of anti-TNF therapy and subsequent clinical outcomes. A Dutch group found that MTX reduced immunogenicity to IFX in a dose-dependent manner, with the odds of developing antidrug antibodies being 0.36 (95% CI, 0.18–0.74) in the 5 to 10 mg/wk, 0.22 (95% CI, 0.10–0.46) in the 12.5 to 20 mg/wk, and 0.14 (95% CI, 0.07–0.28) in patients on >22.5 mg/wk relative to patients not treated with MTX.[35] In addition, in a post hoc analysis of the SONIC study, patients on combination therapy with AZA with an increase of 7 femtoliters in the mean corpuscular volume (delta MCV), used as a surrogate marker for therapeutic TGN levels, were more likely to achieve mucosal healing (75% versus 47% for delta MCV > 7, $P = 0.017$) and maintain therapeutic trough IFX levels > 3 μg/mL at week 30 (68% versus 39% for delta MCV > 7, $P = 0.003$).[36] Similarly, in a cross-sectional analysis of 72 patients with inflammatory bowel disease,

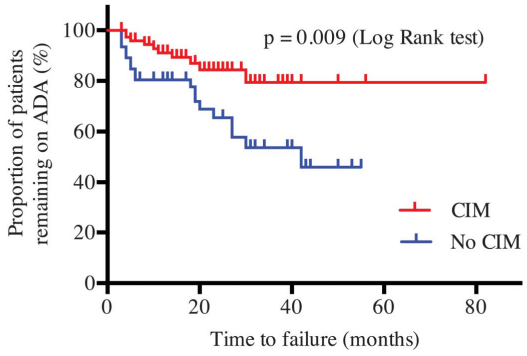

FIGURE 5. Time to adalimumab failure. Kaplan–-Meier analysis illustrating time to ADA failure (months) in patients treated (n = 77) and not treated (n = 46) with CIM for ≥3 months before commencing ADA (and continued for first 6 months).

IFX drug levels were higher among those on combination therapy with a thiopurine compared with IFX monotherapy (13 versus 4.8 μg/mL,), and a TGN cutoff of 125 pmol/8 × 10^8 RBC best predicted a significantly higher IFX trough level.[16] Taken together with the findings that higher anti-TNF drug levels are associated with improved rates of remission,[37,38] these findings suggest that the dose of thiopurine may be of significant importance.

A recent Australia New Zealand Consortium cohort study comparing IFX/ADA with or without IM suggested that corticosteroids used at induction or in the preceding 12 months were associated with 9 to 13 times greater risk of flare semester during maintenance.[39] There was significantly higher use of steroids at induction in the no-CIM arm in the current cohort. However, most of these patients were either intolerant of or failed IM therapy, and steroids were used as a bridge to biological therapy. In addition, there was no difference in steroid use between patients with therapeutic and subtherapeutic TGN levels at induction (21.8% versus 37.5%, $P = 0.07$).

The utility of measuring TGN in patients taking thiopurines as combination therapy is perhaps even greater when one considers rates of nonadherence and the impact of hypermethylation. Adherence to thiopurines is a well-recognized problem in inflammatory bowel disease.[40] Similarly, underdosing with thiopurines has been reported in 29% when weight-based dosing is used.[24] Thiopurine hypermethylation, whereby shunting occurs away from the therapeutic TGNs toward a methylated metabolite profile, is seen in 15% to 20% and is associated with an inability to achieve therapeutic TGN.[41] Without thiopurine metabolite testing, a large proportion of patients will fail to achieve a therapeutic TGN; the structured approach to optimization of thiopurines in our cohort may explain why a greater benefit of CIM was observed compared with other cohorts.

The development of antibodies against ADA has been implicated as a mechanism leading to secondary loss of response and treatment failure.[42,43] Combination therapy can improve the pharmacokinetics of IFX by increasing drug levels[44] and by decreasing anti-IFX antibody production (RR: 0.50, 95% CI, 0.42–0.59, $P < 0.00001$).[44] A recent study demonstrated the beneficial effect of concomitant thiopurine in reducing immunogenicity, regardless of previous clinical response to thiopurines.[45] In a retrospective analysis of 536 samples collected from 148 patients analyzed using a drug-tolerant homogenous mobility shift assay, antibodies to ADA were detected in 20% after a median of 34 weeks.[8] CIM was associated with decreased antibody formation (HR: 0.23, 95% CI, 0.06–0.86), and antibodies were associated with future elevated CRP ($P = 0.0013$) and discontinuation of ADA due to loss of response (OR 3.04, 95% CI, 1.039–9.093). Such immunogenicity occurs early during ADA therapy. A prospective observational cohort study of 272 patients treated with ADA for rheumatoid arthritis found antibodies to ADA in 28% over a 3-year follow-up; in 67% antibodies occurred within the first 28 weeks of therapy.[46] Similarly, antibodies to IFX have also been found to occur early. In a prospective observational study of 125 patients with inflammatory bowel disease, antidrug antibodies occurred in 46% at a median time of 1.5 months (interquartile range 0.5–5.5); 90% developed within 12 months and antidrug antibody free survival was longer in patients taking combination therapy compared with IFX monotherapy ($P = 0.003$).[47] These findings suggest that early CIM, perhaps even before starting anti-TNF therapy is important, as has previously been shown in murine models.[48] Thiopurines have a slow onset of action, with a mean time to response of 3.1 months.[21] Therefore, it is possible that some of the beneficial effects of combination therapy may be greater in those patients who are established on therapy before starting ADA.

Given the findings from our study (and some others) that early combination therapy is beneficial, and that immunogenicity occurs largely in the first 12 months of ADA therapy, a key question is whether combination therapy should be continued during maintenance. Such a decision must weigh up the benefits and risks of continued combination therapy against withdrawal to ADA monotherapy. In this regard, we demonstrated higher rates of remission semesters in those treated with CIM versus ADA monotherapy (81% versus 60%) and in those with therapeutic compared with nontherapeutic TGNs (85% versus 58%). Further, CIM use during a semester was an independent predictor of remission (OR 2.92, 95% CI, 1.62–5.25, $P < 0.0001$). Our results are in agreement with those from the Oxford/Liege cohort, where combination therapy beyond 6 months was associated with fewer semesters with flares (14% versus 36%, $P = 0.02$, OR = 0.31).[15] Recent studies have called into question the benefit of continued CIM during maintenance therapy, suggesting that a lower dose of thiopurine may be equally efficacious as full weight-based dosing.[49] We were unable to explore this association in the current study as only a small proportion of patients (3/65) were found to have TGNs <125. The benefits of combination therapy must, of course, be balanced with the risks particularly in light of recent safety signals regarding the use of thiopurines.[50,51]

TABLE 4. Univariate and Multivariate Predictors of ADA Failure

	Univariate		Multivariate	
Covariant	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex (reference female)	0.42 (0.19–0.93)	0.03	0.39 (0.17–0.91)	0.028
Age at diagnosis	0.99 (0.96–1.04)	0.94		
Disease duration at start of ADA	1.01 (0.97–1.06)	0.60		
Montreal location (reference L3)				
L1	1.74 (0.63–4.80)	0.28		
L2	1.34 (0.55–3.26)	0.51		
Montreal location L4	0.82 (0.45–2.75)	0.82		
Montreal behavior (reference B3)				
B1	0.49 (0.17–1.39)	0.18		
B2	0.84 (0.34–2.09)	0.71		
Perianal disease	1.15 (0.54–2.47)	0.72		
EIM	0.40 (0.12–1.32)	0.13		
Weight (kg)	0.98 (0.95–1.01)	0.18		
Current smoker	1.07 (0.64–1.78)	0.80		
Family history of IBD	0.32 (0.52–2.02)	0.23		
Previous bowel resection	0.73 (0.34–1.55)	0.41		
Previous perianal surgery	1.10 (0.42–2.89)	0.85		
Exposure to anti-TNF	1.19 (0.54–2.60)	0.67		
Steroids at induction	1.61 (0.76–3.42)	0.21		
5-ASA at induction	1.81 (0.73–4.48)	0.20		
CIM induction (reference no-CIM)				
Subtherapeutic TGN	0.31 (0.04–2.38)	0.52	0.42 (0.04–2.38)	0.263
Therapeutic TGN	0.38 (0.16–0.91)	0.03	0.37 (0.15–0.89)	0.026
CRP at induction	1.01 (0.99–1.02)	0.37		
Albumin at induction	0.98 (0.92–1.03)	0.40		
HBI at induction	1.00 (0.91–1.10)	0.99		
ADA dose escalation	0.46 (0.19–1.11)	0.08	Removed	0.203

5-ASA, 5-aminosalicylic acid; EIM, extraintestinal manifestation; IBD, inflammatory bowel disease.

We acknowledge several limitations with the study. First, patients were not randomized to combination therapy or ADA monotherapy; hence, despite the groups being similarly matched in terms of phenotype, previous anti-TNF exposure, and disease severity they are not directly comparable. Second, as we did not measure ADA drug levels or antibodies to ADA, we cannot prove that the benefit seen with CIM was due to improvements in ADA pharmacokinetics and reductions in immunogenicity. Third, assessment of response to induction and during maintenance was made using a combination of HBI, CRP, and fecal calprotectin. Fourth, a relatively high number of patients were treated with corticosteroids during induction (53%) which may contribute to the relatively high response rate seen overall (75%). However, there was no difference in corticosteroid use in patients who had therapeutic and subtherapeutic levels of TGN. Finally, a relatively small proportion of patients had subtherapeutic TGNs during induction (15%) and maintenance (12%); hence, the conclusion that response rates are superior with therapeutic compared with subtherapeutic TGNs should be interpreted with caution until it has been confirmed in other cohorts. We acknowledge that this distribution of TGNs limited our ability to apply further relevant statistical methodology such as a quartile or ROC analysis.

CONCLUSION

Combination therapy was found to be superior to ADA monotherapy in this cohort of patients with moderate-to-severe Crohn's disease with improved response at induction, more semesters in remission, and a longer time to ADA failure. Further, adequately dosed thiopurines when used as CIM were associated with improved clinical outcomes. We propose that, after carefully balancing the risk and benefit and noting the association of increased risks of lymphoma, nonmelanoma skin cancer and possibly other malignancies,[50] immunomodulators should be initiated

early when considering ADA therapy, dosed to a TGN > 235, and continued during maintenance therapy. Further randomized controlled studies are needed that incorporate thiopurine metabolite testing during both induction and maintenance.

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APPENDIX 3 – STUDY 4 – PUBLISHED ARTCLE

ORIGINAL RESEARCH ARTICLE—CLINICAL

Comorbidities Rather Than Age Are Associated With the Use of Immunomodulators in Elderly-onset Inflammatory Bowel Disease

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Background and Aim: The use of immunomodulators (IMs) is often avoided in elderly patients with inflammatory bowel disease (IBD) due to concerns about complications. Our aim is to compare the use of IMs in elderly and younger patients with Crohn's disease (CD) or ulcerative colitis (UC) and identify markers that predict their use.

Methods: In this retrospective cohort study, patients diagnosed with IBD from 1970 to 2009 were recruited from the "Sydney IBD Cohort." Patients diagnosed at age 60 years old or older and between 16 and old 40 years were classified as "elderly-onset" and "young-onset" respectively.

Results: A total of 255 elderly-onset patients (115 CD, 140 UC) and 1244 young-onset patients (657 CD, 587 UC) were recruited. Most elderly-onset patients had colonic CD (61.4%), whereas young-onset patients had predominantly ileocolonic CD (42.8%, $P < 0.0001$). Left-sided UC was the most common disease localization for both elderly-onset (52.1%) and young-onset patients (42.2%, $P = 0.013$). The cumulative probability of IM exposure at 5 years post-diagnosis was significantly less in elderly-onset patients compared with young-onset patients for CD (20.0% vs 33.4%, $P = 0.0002$) and UC (7.8% vs 13.4%, $P = 0.0007$). Age at diagnosis was not associated with the time to IMs introduction. Charlson Comorbidity Index was shown to delay IM introduction in CD (hazard ratio [HR] 0.863; 95% CI, 0.787–0.946; $P = 0.002$) and UC (HR 0.807; 95% CI, 0.711–0.917; $P = 0.001$). Early IM use was associated with reduced need for abdominal and perianal surgery in CD (HR 0.177; 95% CI, 0.089–0.351; $P < 0.0001$).

Conclusions: Comorbidity and not age at diagnosis is associated with IM introduction. Early IM is associated with reduced surgery in both young- and elderly-onset CD but not UC.

Key Words: inflammatory bowel disease; geriatric; elderly; aging; immunomodulators; surgery

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are inflammatory disorders that typically affect the younger age group. Patients age 60 or older comprise only 10%–15% of incident IBD cases.[1, 2] Currently, there are no age-specific treatment guidelines for elderly-onset IBD. Because the natural history of IBD varies according to the age of onset, the current management practices designed for adult patients may not be applicable to the elderly.[3, 4] Presence of comorbidity and polypharmacy in elderly patients further underpins the challenges associated with managing this population[5] at risk of opportunistic infections and cancers.

The conventional treatment practice adopts a "step-up" approach starting with 5-aminosalicylic acid (5-ASA). Thus, most studies are unable to demonstrate the positive effects of immunomodulators (IMs) due to their use in a more severe disease after development of strictures or fistulas or insufficient patient-years of follow-up. Recent evidences demonstrate efficacy in the "top-down" approach, which involves introducing IMs and biologics early in the disease course.[6, 7] This may be more effective in controlling inflammation and preventing irreversible damage to the intestinal mucosa from the first flare-up than the "step-up" approach.[8, 9] Additionally, introduction of IMs early in the disease course has been suggested to delay first major surgery for CD.[6, 10]

Immunomodulators are used to maintain remission in steroid-dependent or refractory patients.[11] Their use in the elderly is tentative due to higher risks of adverse effects and

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opportunistic infections.[12, 13] Immunomodulators can cause adverse events in approximately 15% of patients, and this can be classified into allergic (pancreatitis, fever, rash, and arthralgia) and nonallergic (leukopenia, thrombocytopenia, infection, and hepatitis) reactions. Of a greater concern is the increased risk of malignancy as patients 65 years or older receiving thiopurines were found to be 2.6 times more likely to develop lymphoma than their younger counterparts.[14] Physicians may therefore avoid IMs use in older patients with IBD.

Data on surgical outcome within the elderly-onset IBD patients are scarce. Elderly CD patients undergo surgery less often compared with their younger counterparts, whereas the rates are comparable for elderly UC and adult UC patients.[15] It is unclear whether elderly-onset CD takes a generally milder course or whether physicians have higher threshold for surgical interventions. Elderly patients with IBD experience a higher rate of postoperative morbidity and mortality and an increased length of hospital stay and operation time.[16, 17] Given the preventative effects of IMs on surgery, elderly patients with IBD may benefit from early treatment if those likely to require the therapy could be identified at diagnosis.

We hypothesized that elderly-onset patients with IBD were less likely to receive IMs for IBD and that the decision to avoid IMs is driven by age. The primary study aim therefore was to compare IMs prescription rates between elderly-onset and younger IBD patients with a view to identifying patients characteristics and clinical markers at presentation that predict the initiation of IMs therapy. The secondary outcome was the impact of early IMs use on the requirement of first surgery due to IBD.

MATERIALS AND METHODS

Population

Data of ambulatory patients with IBD from 1942 to 2014 were retrospectively collected from 2 tertiary hospitals and 6 private consultant rooms in Sydney metropolitan region. The Sydney IBD cohort was first described in 1994, and the methodology was repeated in 2010 and 2012 to augment the cohort.[18] Diagnoses were confirmed retrospectively by a review of the clinical and endoscopic reports and radiological, histological, and pathological investigations. To focus on a more recent cohort of patients and with adequate duration of follow-up, only those with a definitive diagnosis of CD or UC between January 1, 1970, and December 31, 2009, were recruited. Patients with indeterminate colitis or those who had a change of diagnosis to a non-IBD pathology were excluded.

Patients were categorized into 2 groups according to their age at diagnosis. The first group of patients who were diagnosed at age 60 or older were classified as "elderly-onset" IBD patients. The second group consisted of patients diagnosed from 16 to 40 years of age and were referred to as "young-onset" IBD patients.

Data Collection

All demographic data in addition to medical therapy and surgical interventions were collected. Clinical records, operation reports, and discharge summaries were reviewed for patient demographics, disease characteristics, use of medications, surgical history, and presence of polypharmacy and comorbidity. Those lost to follow-up were contacted and, if unavailable, were excluded as of their last observation. Disease characteristics were categorized at diagnosis according to the Montreal classification, and any changes with the treatment were updated until the most recent follow-up.

Medical therapy consisted of 5-ASA, corticosteroid, IMs (Azathioprine [AZA], Mercaptopurine [6-MP], and methotrexate [MTX]) and anti-tumour necrosis factor (TNF) alpha agents (adalimumab and infliximab). Long-term steroid use was classified as ≥6 months of continuous use of steroids within a 12-month period. Those who used either AZA, 6-MP, or MTX continuously for 6 months were considered as being "maintained" by IMs. Early IM use was defined as introduction of an IM within 3 years of diagnosis and being on the medication continuously for ≥6 months.[6]

Patients' comorbid statuses were quantitatively expressed using the Charlson comorbidity index (CCI)[19] at the time of diagnosis. Rate of hospitalization was calculated by dividing the total number of IBD-related hospital admissions by the duration of follow-up. Details of major abdominal, perianal, or resectional surgeries were recorded. Simple surgical interventions under anesthesia without abscess drainage were excluded.

Treatment Practices

Throughout the study period, thiopurines were used as the first IM of choice, with AZA used more preferentially than 6-MP. Typical dosing of AZA was 2 to 2.5 mg/kg body weight, and for 6-MP, it was 1 to 1.5 mg/kg body weight. Consistent with the national guidelines, MTX replaced AZA/6-MP when a patient became intolerant to the drug. Patients with thiopurine methyltransferase deficiency or arthritic extraintestinal manifestation were initiated on MTX immediately. Methotrexate was prescribed at an initial dose of 25 mg per week with maintenance dosing of 15 mg per week thereafter, taken either orally or parenterally. Immunomodulator therapy was ceased in cases of failure, adverse events, patient noncompliance, pregnancy, and/or other patient circumstances. Otherwise, once initiated IMs were prescribed continuously.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software version 23.0. Qualitative data were reported as percentages and were analyzed using χ^2 test. Continuous variables were described using either median and interquartile range (IQR) and analyzed with the Mann-Whitney *U* test if nonparametrically

distributed. Normally distributed continuous variables were described using mean and standard deviation and analyzed using the *t* test. A *P* value of <0.05 was considered statistically significant.

Survival analyses of the IM introduction and surgery were calculated using the log-rank score and were displayed on the Kaplan-Meier curve. Hazard ratios (HR) were calculated using Cox proportional hazards regression models (both univariate and multivariate) with 95% confidence intervals (CI) when determining predictors of IM exposure and surgery. All baseline characteristics at diagnosis, medication use, comorbidity, and polypharmacy were tested using the univariate analysis. Any variables with *P* value less than 0.1 were included into the multivariate analysis.

Ethical Consideration

Ethics approval was obtained from the Sydney Local Health District Human Research Ethics Committee (HREC/10/CRGH/126).

RESULTS

Patient Demographics

A total of 255 elderly-onset (115 CD, 140 UC) patients and 1244 young-onset (657 CD, 587 UC) patients were recruited (Table 1). The median duration of follow-up was 8.0 (interquartile range [IQR] 3.0–13.0) for the elderly-onset group and 11.0 (IQR 5.0–20.0) for the young-onset group for CD ($P < 0.0001$). For UC, the median duration of follow-up was 8.0 (IQR 3.0–14.8) for the elderly-onset group and 11.0 (IQR 4.0–20.0) for the young-onset group ($P < 0.0001$).

The ileocolonic CD phenotype was the commonest location in young-onset patients (42.8%), whereas colonic CD was found in 61.4% of elderly-onset patients ($P < 0.0001$). In UC, left-sided location was the commonest location for both young-onset (42.2%) and elderly-onset groups (52.1%, $P = 0.013$).

Medical Interventions

A significantly lower proportion of elderly-onset CD patients compared with young-onset CD patients were exposed to (24.5% vs 49.7%, $P < 0.0001$) and maintained on (19.0% vs 42.5%, $P < 0.0001$) immunomodulators (Table 2). In UC, IM exposure (8.1% vs 20.5%, $P = 0.001$) and IM maintenance (5.2% vs 16.5%, $P = 0.001$) were considerably lower in elderly-onset vs young-onset groups, respectively (Table 2). In UC, early IM use was significantly lower in the elderly-onset (3.0%) vs the young-onset group (7.8%, $P = 0.048$). Thiopurine was the commonest IM prescribed to both elderly-onset and young-onset groups in CD and UC.

In CD, the cumulative probability of IM exposure at 5 years after diagnosis was 20.0% in elderly-onset patients vs 33.4% in young-onset patients ($P = 0.002$, Fig. 1). In UC, the cumulative probability of IM exposure at 5 years after diagnosis was 7.8% in elderly-onset patients and 13.4% in young-onset patients ($P = 0.007$, Fig. 1).

Comorbidity, Polypharmacy, and Rate of Hospitalization

Elderly-onset subjects had significantly higher comorbidities than young-onset subjects in both CD (median CCI: 5.0 [IQR: 2.0–6.0] vs median CCI: 0.0 [IQR: 0.0–1.0], respectively; $P < 0.0001$) and UC (median CCI: 5.0 [IQR: 4.0–7.0] vs median CCI: 1.0 [IQR: 0.0–2.0], respectively; $P < 0.0001$). Pearson correlation analysis was performed between age and CCI. Correlation was 0.58 ($P < 0.0001$) in the CD cohort and 0.79 ($P < 0.0001$) in the UC cohort.

The median total number of medications taken was 8.0 (IQR 4.75–9.25) by elderly-onset CD patients compared with 2.0 (IQR 1.0–3.0) for young-onset CD patients. For UC, the median was 6.0 (IQR 3.0–9.0) for elderly-onset and 2.0 (IQR 1.0–3.0) and young-onset groups ($P < 0.0001$). Elderly-onset patients were admitted to the hospital more frequently than young-onset patients for both CD and UC. In CD, there were 0.23 ± 0.40 hospital admissions per year in young-onset patients and 0.41 ± 0.82 hospital admissions per year in elderly-onset patients ($P = 0.023$). Young-onset UC patients were admitted 0.09 ± 0.26 times per year, whereas elderly-onset UC patients were admitted 0.23 ± 0.54 times per year ($P < 0.0001$).

Factors Affecting Time to Initiation of IM Therapy

For both UC and CD, age of diagnosis was not associated with the time at which IMs were introduced (Tables 3 and 4). In CD, CCI was significantly associated with delayed introduction of IM (HR: 0.86; 95% CI, 0.79–0.95; $P = 0.002$). Out of the baseline characteristics considered, only extra-intestinal manifestation was associated with early introduction of IM (HR: 1.47; 95% CI, 1.01–2.14; $P = 0.042$). Long-term steroid use (HR: 1.91; 95% CI, 1.42–2.58; $P < 0.0001$), anti-TNF use (HR: 1.68; 95% CI, 1.20–2.34; $P = 0.003$) and number of hospital admissions per year (HR: 1.49; 95% CI, 1.22–1.81; $P < 0.0001$) were associated with the need for earlier IM therapy.

In UC, multivariate analysis revealed that having higher CCI predicted for delayed use of IM (HR: 0.81; 95% CI, 0.71–0.92; $P = 0.001$). Proctitis (HR: 0.45; 95% CI, 0.23–0.89, $P = 0.021$) was associated with delayed initiation of IMs compared with pancolitis. Long-term steroid use (HR: 4.45; 95% CI, 2.69–7.36; $P < 0.0001$), anti-TNF exposure (HR: 2.12; 95% CI, 1.03–4.40; $P = 0.042$) and number of hospital admissions per year (HR: 2.21; 95% CI, 1.24–3.94; $P = 0.007$) were associated with the need for earlier IM therapy.

TABLE 1. Demographics and Clinical Characteristics of Crohn's Disease and Ulcerative Colitis Patients at Diagnosis

	Crohn's Disease			Ulcerative Colitis		
	Young-onset (16–40)	Elderly-onset (≥60)	*P*	Young-onset (16–40)	Elderly-onset (≥60)	*P*
No. patients	657	115		587	140	
Median age (IQR)	26 (22–31.5)	68 (64–76)	<0.0001	28 (24–33)	67 (64–74)	<0.0001
Median follow-up (IQR)	11 (5–20)	8 (3–13)	<0.0001	11 (4–20)	8 (3–14.8)	<0.0001
Patient-years of follow-up	8589	1002		7824	1327	
Gender, N (%)			0.295			0.048
Male	280 (42.6)	43 (37.4)		285 (48.6)	81 (57.9)	
Female	377 (57.4)	72 (62.6)		302 (51.4)	59 (42.1)	
Disease location, N (%)			<0.0001			
Ileal (L1)	161 (24.8)	15 (13.2)				
Colonic (L2)	211 (32.5)	70 (61.4)				
Ileocolonic (L3)	278 (42.8)	29 (25.4)				
Not documented	7	1				
Upper GI (L4), N (%)			0.181			
Yes	10 (1.5)	0 (0.0)				
No	637 (98.5)	114 (100)				
Not documented	10	1				
Disease phenotype, N (%)			0.947			
Inflammatory (B1)	427 (66.5)	78 (67.8)				
Stricturing (B2)	144 (22.4)	26 (22.6)				
Penetrating (B3)	70 (10.9)	11 (9.6)				
Not documented	15	0				
Perianal disease, N (%)			0.265			
Yes	126 (19.3)	17 (14.9)				
No	526 (80.7)	97 (85.1)				
Not documented	5	1				
Disease location, N (%)						0.013
Proctitis (E1)				201 (34.2)	30 (21.4)	
Left-sided (E2)				248 (42.2)	73 (52.1)	
Pancolitis (E3)				138 (23.5)	37 (26.4)	
Not documented				0	0	
Extra-intestinal, N (%)			0.787			0.509
Yes	117 (18.9)	22 (20.0)		90 (15.6)	18 (13.3)	
No	502 (81.1)	88 (80.0)		487 (84.4)	117 (86.7)	
Not documented	38	5		10	5	

Factors Affecting Time to First IBD-Related Surgery

The 10-year cumulative probability of undergoing major abdominal or perianal surgery for CD was 27.0% for elderly-onset patients vs 42.7% for young-onset patients ($P = 0.003$, Fig. 2). Median time to first surgery was 5.0 years (IQR: 2.0–11.2) for young-onset patients and 5.5 years (IQR: 2.0–10.0) for elderly-onset patients ($P = 0.477$). Multivariate analysis revealed that early IM use was associated with delayed need for surgery (HR: 0.18; 95% CI, 0.09–0.35; $P < 0.0001$, Table 3). Patients with colonic CD (HR: 0.25; 95% CI, 0.13–0.48; $P < 0.0001$) were less likely to require surgery than ileocolonic CD. Patients with the inflammatory phenotype (HR: 0.44; 95% CI, 0.26–0.74; $P = 0.002$) were less likely to have early surgery than those with the penetrating phenotype. Frequent hospitalization was also an indicator for earlier surgery (HR: 1.48; 95% CI, 1.23–1.77; $P < 0.0001$).

For UC, the 10-year cumulative probability of undergoing colectomy was 10.9% for elderly-onset patients and 5.9% for young-onset patients ($P = 0.22$, Fig. 2). Median time to first intestinal resection was 7.0 years (IQR: 3.0–13.0) for elderly-onset patients vs 11.0 years (IQR: 4.0–20.0) for young-onset patients ($P < 0.0001$). On multivariate analysis, proctitis (HR: 0.18; 95% CI, 0.07–0.48; $P = 0.001$) and

TABLE 2. Medication Use in Crohn's Disease and Ulcerative Colitis Patients During Follow-up

	Crohn's Disease			Ulcerative Colitis		
	Young-onset (16–40) n = 657	Elderly-onset (≥60) n = 115	*P*	Young-onset (18–40) n = 587	Elderly-onset (≥60) n = 140	*P*
5-ASA (%)	538 (86.9)	94 (87.0)	0.972	559 (96.9)	139 (99.3)	0.112
Long-term steroids (%)	384 (60.8)	63 (57.3)	0.490	218 (37.1)	45 (32.1)	0.361
Anti-TNF (%)	66 (10.6)	3 (2.7)	0.009	17 (2.9)	1 (0.7)	0.142
IMs exposure (%)	309 (49.7)	27 (24.5)	<0.0001	118 (20.5)	11 (8.1)	0.001
IMs maintenance (%)	251 (42.5)	20 (19.0)	<0.0001	95 (16.5)	7 (5.2)	0.001
Early IM use (%)	147 (24.9)	18 (17.1)	0.086	45 (7.8)	4 (3.0)	0.048
Exposed IM Type (%)			0.001			0.845
Thiopurine	268 (86.7)	21 (77.8)		117 (92.9)	11 (91.7)	
MTX	1 (0.3)	2 (7.4)		2 (1.6)	0 (0.0)	
Both	40 (12.9)	4 (14.8)		7 (5.6)	1 (8.3)	
Median time to starting IMs, yr (IQR)	6.0 (2.0–16.0)	6.0 (1.5–13.0)	0.220	9.0(3.0–20.0)	8.0 (3.0–15.0)	0.077

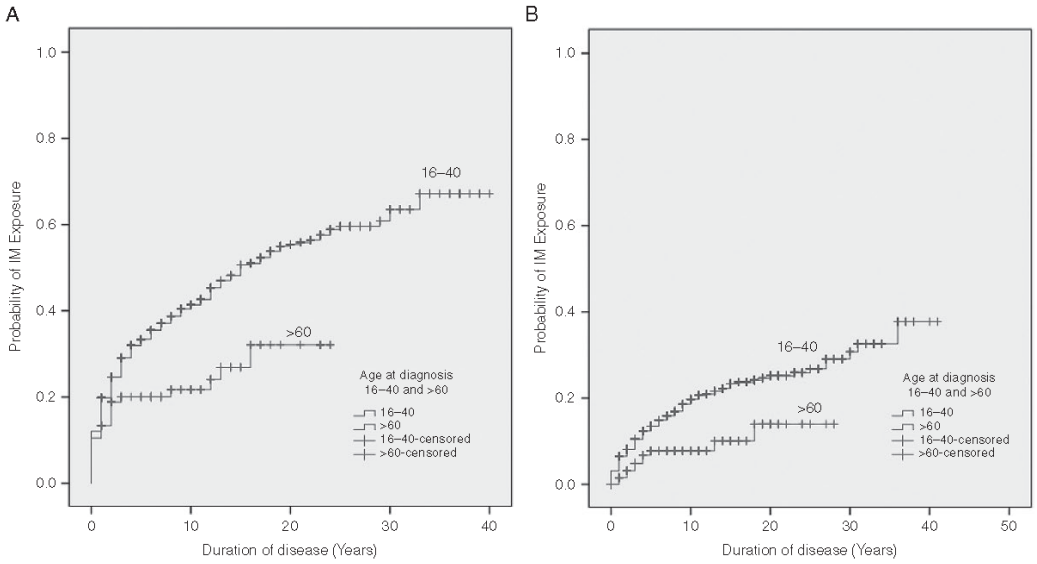

FIGURE 1. Cumulative probability of IM exposure over time since diagnosis in elderly-onset and young-onset patients with CD (1a, $P = 0.002$) and UC (1b, $P = 0.007$).

left-sided UC (HR: 0.29; 95% CI, 0.16–0.54; $P < 0.0001$) were less likely to require a surgery than pancolitis (Table 4). Long-term steroid use (HR: 3.45; 95% CI, 1.85–6.43; $P < 0.0001$), anti-TNF use (HR: 8.17; 95% CI, 2.74–24.42; $P < 0.0001$) and the number of hospital admissions per year (HR: 3.05; 95% CI, 1.95–4.76; $P < 0.0001$) were predictors for early surgery. Early IM use was not a significant predictor of colectomy on the univariate model.

DISCUSSION

In this cohort study, we examined the factors driving the use of IMs for IBD in eldery-onset vs young-onset patients with

TABLE 3. Univariate and Multivariate Predictors of Time to Initiation of IM Therapy and Time to Surgery in Crohn's Disease Patients

Covariant	Time to Initiation of IM Therapy				Time to Surgery			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender	0.94 (0.75–1.18)	0.59			1.18 (0.93–1.50)	0.18		
Age groups	0.53 (0.35–0.80)	0.003		0.45	0.54 (0.35–0.82)	0.004		0.86
Disease location		0.55				<0.0001		<0.0001
Ileal (L1)	0.86 (0.64–1.15)	0.31			1.36 (1.05–1.77)	0.02	1.21 (0.82–1.78)	0.33
Colonic (L2)	0.90 (0.70–1.17)	0.45			0.29 (0.20–0.40)	<0.0001	0.25 (0.13–0.48)	<0.0001
Ileocolonic (L3)	Reference				Reference			
Disease phenotype		0.63				<0.0001		0.001
Inflammatory (B1)	0.84 (0.59–1.20)	0.34			0.29 (0.20–0.40)	<0.0001	0.44 (0.26–0.74)	0.002
Stricturing (B2)	0.88 (0.58–1.31)	0.52			0.90 (0.63–1.29)	0.57	0.89 (0.52–1.51)	0.66
Penetrating (B3)	Reference				Reference			
Perianal involvement	1.64 (1.27–2.12)	<0.0001		0.30	0.88 (0.64–1.21)	0.43		
Extra-intestinal	1.35 (1.02–1.78)	0.04	1.47 (1.01–2.14)	0.04	0.76 (0.55–1.06)	0.10		
5-ASA use	0.85 (0.61–1.18)	0.33			0.57 (0.41–0.79)	0.001		0.13
Long-term steroids use	1.45 (1.13–1.85)	0.003	1.91 (1.42–2.58)	<0.0001	1.58 (1.21–2.08)	0.001	1.70 (1.17–2.48)	0.006
Anti-TNF use	3.79 (2.88–4.99)	<0.0001	1.68 (1.20–2.34)	0.003	1.03 (0.69–1.53)	0.89		
CCI	0.87 (0.80–0.95)	0.002	0.86 (0.79–0.95)	0.002	0.23 (0.13–0.40)	<0.0001	0.18 (0.09–0.35)	<0.0001
No. medications	1.01 (0.96–1.05)	0.83			1.08 (0.99–1.17)	0.07		
CD-related surgery	0.99 (0.79–1.24)	0.92			1.04 (0.98–1.10)	0.17		
No. hospital admissions per year	1.53 (1.33–1.75)	<0.0001	1.49 (1.22–1.81)	<0.0001	1.58 (1.36–1.83)	<0.0001	1.48 (1.23–1.77)	<0.0001

IBD. In contrast to our hypothesis, age-related factors including comorbid status rather than age itself were associated with IM use. Comorbidity was shown to delay the time at which IMs were introduced in both CD and UC, whereas age at diagnosis was not associated with IM introduction. Physicians, therefore, did not base IM treatment on age alone. Comorbidities influenced the use of IMs, and therefore the overall use of IMs was significantly lower in elderly-onset IBD patients than in young-onset IBD patients.

The decrease rate in IM prescriptions in the elderly is consistent with many studies.[15, 20–22] It is often hypothesized that this difference in utilization may have been due to lower disease severity in the elderly, particularly for CD.[23] In contrast to other studies, we found that elderly onset patients may also experience severe disease: the rates of hospitalizations, for examples, were higher for elderly-onset IBD patients than those of the young-onset cohort. The requirement for surgery was greater for elderly-onset patients with UC, and although fewer elderly-onset patients with CD required surgery, the time to surgery was similar to that of young-onset patients. Based on our data, it is therefore questionable whether elderly-onset IBD per se is prone to take a milder course.

Elderly patients experience complications associated with IMs more frequently than younger patients, contributing to their lesser use.[14, 24, 25] Although steroid dependence has been shown to be more common in the elderly,[26] this was not seen in our cohort in which long-term steroid usage was similar between the 2 age groups. Steroid-sparing IMs, therefore, might be advantageous in the elderly IBD patients despite the potential for side effects,[14, 27, 28] which are more common in the elderly. These side effects should be put in the balance when prescribing these drugs to the elderly who are frail and less able to tolerate severe or prolonged periods of disease activity.[29] Our study showed no difference between the 2 groups in the proportion of patients who stopped the IM after being initiated. Although the exact reasons are not available, we assume that side effects constitute an important cause for discontinuing the drug.

Comorbidity is an exemplary age-related factor that is more prevalent in the elderly than in younger populations. Most studies on elderly-onset IBD fail to acknowledge the importance of comorbidity when assessing patients' treatment outcomes. While this study confirms the lesser use of IMs within the elderly, age of diagnosis itself was not a factor that restricted the use of IMs. Instead, it is comorbidity that delayed the initiation of IM therapy. Comorbidity can alter the prognosis of IBD and increase the likelihood of drug-to-drug interaction.[5] Thus, it appears that physicians base their decisions

TABLE 4. Univariate and Multivariate Predictors of Time to Initiation of IM Therapy and Time to Surgery in Ulcerative Colitis Patients

Covariant	Time to Initiation of IM Therapy				Time to Surgery			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender	0.74 (0.53–1.05)	0.096		0.67	0.72 (0.42–1.22)	0.22		
Age groups	0.44 (0.24–0.82)	0.010		0.12	1.49 (0.78–2.84)	0.22		
Disease location		<0.0001		0.066		<0.0001		<0.0001
Proctitis (E1)	0.30 (0.17–0.54)	<0.0001	0.45 (0.23–0.89)	0.021	0.11 (0.04–0.28)	<0.0001	0.18 (0.07–0.48)	0.001
Left-sided (E2)	1.04 (0.71–1.53)	0.83			0.27 (0.15–0.49)	<0.0001	0.29 (0.16–0.54)	<0.0001
Pancolitis (E3)	Reference				Reference			
Extra-intestinal	1.32 (0.86–2.02)	0.20			1.26 (0.66–2.39)	0.48		
5-ASA use	20.94 (0.18–2495)	0.21			20.91 (0.01–32271)	0.42		
Long-term steroids use	4.90 (3.30–7.27)	<0.0001	4.45 (2.69–7.37)	<0.0001	4.40 (2.43–7.94)	<0.0001	3.45 (1.85–6.43)	<0.0001
Anti-TNF use	9.48 (5.65–15.92)	<0.0001	2.12 (1.03–4.40)	0.04	4.29 (1.70–10.80)	0.002	8.17 (2.74–24.42)	<0.0001
CCI	0.78 (0.68–0.90)	0.001	0.81 (0.71–0.92)	0.001	0.36 (0.05–2.60)	0.31		
No. medications	1.02 (0.97–1.08)	0.42			0.82 (0.56–1.20)	0.31		
UC-related surgery	1.25 (0.75–2.08)	0.40			0.98 (0.83–1.16)	0.83		
No. hospital admissions per year	2.15 (1.66–2.79)	<0.0001	2.21 (1.24–3.95)	0.007	5.45 (3.58–8.29)	<0.0001	3.05 (1.95–4.76)	<0.0001

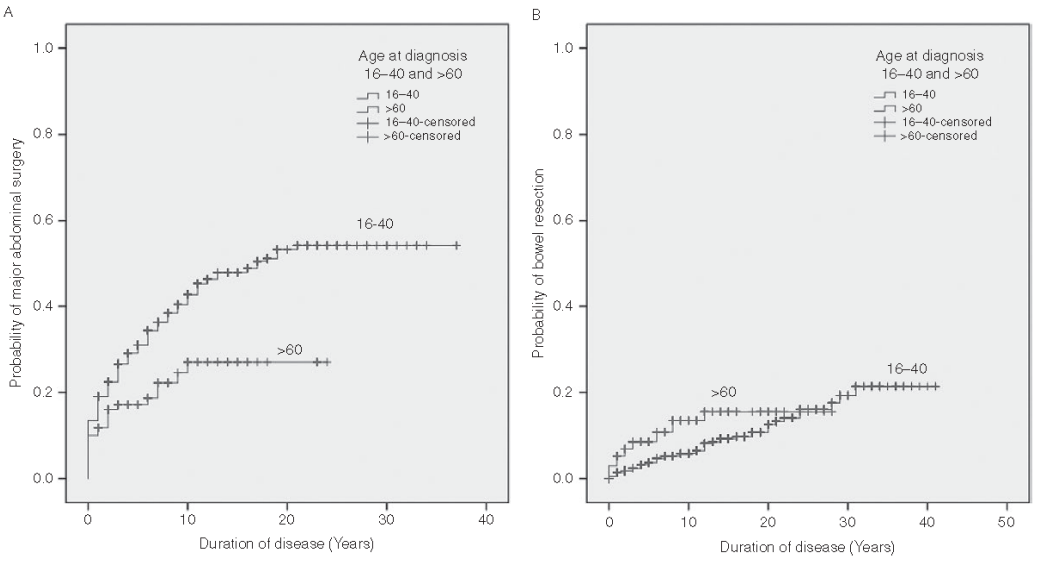

FIGURE 2. Cumulative probability of first IBD-related surgery since diagnosis in elderly-onset and young-onset patients with CD (2a, $P = 0.003$) and UC (2b, $P = 0.219$).

in elderly-onset patients appropriately on comorbidity rather than age.

Fewer elderly-onset CD patients underwent surgery compared with young-onset CD patients. In UC, the opposite was observed until 20 years after diagnosis, at which point the probability converged for the two groups. Two factors may contribute to this observation. First, given that more elderly-onset patients presented with left-sided or pancolitic UC, elderly-onset UC may progress as a more aggressive disease than young-onset UC. The fact that pancolitis is associated with increased risk of colectomy may also support this finding. Secondly, surgical risk is highest among patients with ileal or ileocolonic disease.[6] Thus, without being curative, surgery in the elderly CD is less imperative and potentially harmful due to higher risk of postoperative complications and longer hospital stay.[16, 17] Surgery for UC, however, is curative, and thus physicians and patients may prefer a more definite surgical intervention than long-term IM therapy. Likewise, a Pennsylvanian study by Juneja et al[15] found that patients with CD diagnosed younger than 65 years of age were more likely to undergo surgery than those diagnosed at 65 years or older. However, the UC colectomy rate in this cohort was similar between the 2 groups.

The recommended clinical practice is evolving towards the "top-down" approach with early initiation of immunosuppressive therapy. Such therapy ensures patients' quality of life throughout the disease course and is more efficacious in inducing remission than the conventional approach.[7] We observed that early IM use (≤3 years since diagnosis) is associated with a delay in major abdominal or perianal surgery for CD. This was seen even among elderly-onset patients, despite having a lower surgical rate and lower use. This observation has also been made by other studies.[6, 7, 30] This indicates that healthy elderly-onset patients with minimal comorbidities should be considered for early IM therapy to prevent future surgical risk. Similar finding was not displayed for UC, possibly due to smaller number of patients receiving IM.

The strengths of this study include its abundant patient-years of follow-up and complete record of disease characterisation at diagnosis. The present study followed the standardized management regimes and case definitions that may be lacking in studies derived from insurance data, hospital coding, or de-identified data. The Montreal Classification system, which is an objective marker of disease severity, was employed to prevent bias associated with recall or misclassification. Such strategies were adopted in other Australian and New Zealand population-based studies. Most importantly, this was one of the few studies that identified age and age-related factors as separate variables when determining predictors of time to IM introduction.

There are a few limitations to this study. It is a retrospective study based on an ambulatory specialist-referred cohort within the Sydney Local Health District. This mode of data acquisition and geographic isolation may have exposed the study to selection bias. However, recruitment of patients managed by gastroenterologists with exceptional longitudinal follow-up and documentation allowed precise characterization of every cause and ensured the definition of IM was met. Secondly, our data were affected by changes in treatment practices and governmental regulations over the past decades. This may account for the smaller number of patients receiving biologics within the population.

In conclusion, young-onset IBD and elderly-onset IBD showed a distinct difference in disease phenotypes and medication use. Our study showed that in clinical practice, age does not have a correlation with the time at which IMs are introduced, but age-related factors, especially comorbidities, are used instead to assess the appropriateness of IM therapy. Further research into the effects of comorbidity on efficacy and safety of IMs is required. Furthermore, newer agents such as gut-directed therapy with Vedolizumab and potentially fewer side effects may prove a safer option for elderly-onset patients in future. Meanwhile, IMs should be prescribed with care in patients with high comorbid status, regardless of their age or severity of disease. Elderly patients who are fit and healthy should be considered for earlier use of IMs in their disease course for maximal quality of life and to reduce risk of surgery.

ABBREVIATIONS

AZA, Azathioprine; CCI, Charlson comorbidity index; IMS, Immunomodulators; 6-MP, Mercaptopurine; MTX, Methotrexate

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APPENDIX 4 - OTHER PUBLICATIONS DURING THE DOCTORAL PROGRAM.

AP&T Alimentary Pharmacology and Therapeutics

Smoking prevalence and its influence on disease course and surgery in Crohn's disease and ulcerative colitis

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SUMMARY

Background
Smoking demonstrates divergent effects in Crohn's disease (CD) and ulcerative colitis (UC). Smoking frequency is greater in CD and deleterious to its disease course. Conversely, UC is primarily a disease of nonsmokers and ex-smokers, with reports of disease amelioration in active smoking.

Aim
To determine the prevalence of smoking and its effects on disease progression and surgery in a well-characterised cohort of inflammatory bowel diseases (IBD) patients.

Methods
Patients with smoking data of the Sydney IBD Cohort were included. Demographic, phenotypic, medical, surgical and hospitalisation data were analysed and reported on the basis of patient smoking status.

Results
1203 IBD patients were identified comprising 626 CD and 557 UC with 6725 and 6672 patient-years of follow-up, respectively. CD patients were more likely to smoke than UC patients (19.2% vs. 10.2%, $P < 0.001$). A history of smoking in CD was associated with an increased proportional surgery rate (45.8% vs. 37.8%, $P = 0.045$), requirement for IBD-related hospitalisation ($P = 0.009$) and incidence of peripheral arthritis (29.8% vs. 22.0%, $P = 0.027$). Current smokers with UC demonstrated reduced corticosteroid utilisation (24.1% vs. 37.5%, $P = 0.045$), yet no reduction in the rates of colectomy (3.4% vs. 6.6%, $P = 0.34$) or hospital admission ($P = 0.25$) relative to nonsmokers. Ex-smokers with UC required proportionately greater immunosuppressive (36.2% vs. 26.3%, $P = 0.041$) and corticosteroid (43.7% vs. 34.5%, $P = 0.078$) therapies compared with current and never smokers.

Conclusions
This study confirms the detrimental effects of smoking in CD, yet failed to demonstrate substantial benefit from smoking in UC. These data should encourage all patients with IBD to quit smoking.

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Thioguanine in inflammatory bowel disease: Long-term efficacy and safety

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Abstract

Background: Thioguanine (TG) is efficacious in inflammatory bowel disease (IBD), but its toxicity, particularly nodular regenerative hyperplasia (NRH) of the liver, has limited its use. We assessed the long-term clinical outcomes and safety of TG in patients whom were intolerant or refractory to conventional immunomodulators.

Methods: This is a retrospective, single-centre study of IBD patients treated with TG from 2001–2013. Response was defined as clinical remission (Harvey–Bradshaw Index < 5 for Crohn's disease (CD), Simple Clinical Colitis Activity Index < 4 for ulcerative colitis (UC)) without corticosteroids or, if receiving anti-tumour-necrosis-factor (anti-TNF) therapy, absence of dose escalation. We recorded TG failure, withdrawal and adverse events. Patients were monitored with biochemistry, liver biopsy and/or magnetic resonance imaging (MRI).

Results: 54 patients (47 CD and 7 UC) whom received TG (mean dose: 27 mg/d (range: 20–40 mg/d)) as monotherapy ($n = 36$) or concomitantly with anti-TNF ($n = 18$) for a median inter-quartile range of 16 (5–37) months (126 patient-years of follow-up). 32 (59%) patients responded to TG at 6 months and 23 (43%) at 12 months. Pancreatitis did not recur amongst the 19 patients with prior thiopurine-induced pancreatitis. 16 (30%) patients ceased TG due to intolerance or toxicity (four serious); NRH was not observed. 6-thioguanine nucleotide concentrations did not correlate with efficacy nor with toxicity.

Conclusions: TG was efficacious and well tolerated in one out of two patients who had previously failed conventional immunomodulators. NRH did not occur.

Keywords

Crohn's disease, thioguanine, thiopurine, toxicity, ulcerative colitis

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Introduction

Immunomodulation remains the first-line therapy in inflammatory bowel disease (IBD). The conventional thiopurines, azathioprine (AZA) and 6-mercaptopurine (MP), are efficacious in maintaining steroid-free remission in IBD.[1] A substantial proportion of patients with Crohn's disease (CD) require treatment with a thiopurine; however, approximately 20–30% of these patients discontinue due to intolerance.[2] A further 30–40% withdraw treatment due to non-response, in part because an effective therapeutic dose measured by 6-thioguanine nucleotides (TGNs) cannot be achieved.[3] Pharmacogenetic differences in thiopurine metabolism contribute to intolerance and non-response.[4]

After ingestion, AZA is converted to MP, which then undergoes metabolism via the purine salvage pathway, to pharmacologically-active TGN. Concurrently, competitive metabolism by reduction to thiouric acid (via xanthine oxidase) and methylation to

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ORIGINAL CONTRIBUTION

Major Abdominal and Perianal Surgery in Crohn's Disease: Long-term Follow-up of Australian Patients With Crohn's Disease

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BACKGROUND: Most patients with Crohn's disease still require surgery despite significant advances in medical therapy, surveillance, and management strategies.

OBJECTIVE: The purpose of this study was to assess surgical strategies and outcomes in Crohn's disease, including surgical recurrence and emergency surgery.

DESIGN: This was a multicenter, retrospective review of a prospectively collected database.

SETTINGS: A specialist-referred cohort of patients with Crohn's disease between 1970 and 2009 was studied.

PATIENTS: Included were 972 patients with Crohn's disease who were referred to the Sydney Inflammatory Bowel Disease cohort database.

MAIN OUTCOME MEASURES: Main outcomes of interest were the rates of major abdominal and perianal surgery between decades (1970–1979, 1980–1989, 1990-1999, and 2000-2009), indications for surgery, types of procedure performed, rate of elective and emergency surgery, risk of surgical recurrence, and predictive factors for surgery.

RESULTS: Between 1970 and 2009, the overall risks of surgery within 5, 10, and 15 years of diagnosis were 31.7%, 43.3%, and 48.4%. The median time to first surgery from time of diagnosis was 2 years (range, 0–31 years). A total of 6.7% of patients required emergency surgery within 5 years of diagnosis. In total, 8.8% of patients required emergency surgery within 15 years. The overall risk of surgical recurrence was 35.9%. The risk of major abdominal surgery significantly decreased between 2000 and 2009 when compared with the 1970 to 1979 period (OR = 0.49 (95% CI, 0.34–0.70). However, the rate of perianal surgery significantly increased (OR = 5.76 (95% CI, 2.54–13.06)). The main indications for surgery were enteric stricture or obstruction, perianal disease, and intra-abdominal fistulas/abscess. Of the 972 patients over 4 decades, only 11 patients (1.1%) were diagnosed with colorectal cancer.

LIMITATIONS: This was a specialist-referred cohort, not a population-based study.

CONCLUSIONS: The rate of major abdominal surgery has decreased, with surgery reserved for more severe and complicated disease. The natural history of patients with

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