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REVIEW

Impact of thiopurines and anti-tumour necrosis factor therapy on hospitalisation and long-term surgical outcomes in ulcerative colitis

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory condition affecting the large bowel and is associated with a significant risk of both requirement for surgery and the need for hospitalisation. Thiopurines, and more recently, anti-tumour necrosis factor (aTNF) therapy have been used successfully to induce clinical remission. However, there is less data available on whether these agents prevent long-term colectomy rates or the need for hospitalisation. The focus of this article is to review the recent and pertinent literature on the long-term impact of thiopurines and aTNF on long-term surgical and hospitalisation rates in UC. Data from population based longitudinal research indicates that thiopurine therapy probably has a protective role against colectomy, if used in appropriate patients for a sufficient duration. aTNF agents appear to have a short term protective effect against colectomy, but data is limited for longer periods. Whereas there is insufficient evidence that thiopurines affect hospitalisation, evidence favours that aTNF therapy probably reduces the risk of hospitalisation within the first year of use, but it is less clear on whether this effect continues beyond this period. More structured research needs to be conducted to answer these clinically important questions.

Key words: Immunomodulator; Azathioprine; Anti-tumour necrosis factor; Thiopurine; Ulcerative colitis; Hospitalisation; Surgery; Colectomy; Admission

Core tip: Longitudinal population data indicates a protective effect of thiopurines on colectomy in ulcerative colitis in the long-term, but there is limited evidence that they reduce hospitalisation. Research on anti-tumour necrosis factor therapy shows a possible short-term protective effect against colectomy, but more data is needed to address any long-term benefits.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing and remitting bowel condition that presents with recurrent episodes of colonic inflammation, manifesting as periods of prolonged bloody diarrhoea. Despite advances in pharmacological therapies for UC, there is still no known medical cure, and the condition is associated with a considerable risk of surgery[1]. Moreover, the disease process is often associated with the need for hospitalisation, usually during acute flares. Hospitalisation has been correlated with lower health related quality of life in inflammatory bowel disease (IBD) patients[2], and is possibly the most costly aspect for healthcare providers in the long-term management of patients with IBD[3]. As both hospitalization and surgery are objectively identifiable and clinically important events in the natural history of UC, they make attractive clinical endpoints, particularly when addressing the efficacy of UC specific drugs.

The first clinical trials assessing thiopurines in UC are over thirty years old[4], but these drugs [including azathioprine (AZA) and 6-mercaptopurine (6MP)] are now established as effective steroid sparing agents in the maintenance of remission in UC, and are advocated in national and international guidelines[5-7]. Over the past decade, the use of anti-tumour necrosis factors (aTNF), including infliximab and adalimumab, has impacted greatly on the management Crohn's disease, and more recently in UC[8,9] but their role in altering long-term outcomes, in particular surgery and hospitalisation, is less well characterised.

This review focuses on the impact of thiopurines and aTNF therapy on long-term surgical outcomes and hospitalisation in patients with UC. The definition of "long-term" is not easily quantifiable, but for the purposes of the review, we will be primarily considering research that focuses on these two outcomes at one year or later from pharmacological intervention.

SURGERY

Requirement for colectomy is a key endpoint in UC. Some evidence suggests colectomy rates are decreasing. In a large European cohort studied over 30 years, the cumulative probability of surgery at 9 years in UC fell from 14.5% in patients diagnosed between 1979-1986 to 9.1% in patients diagnosed between 2003-2011[10]. A recent systematic review and meta-analysis indicated that colectomy rates within 10 years of diagnosis have decreased over the past 20 years, with an estimated 10 year risk of colectomy in UC of approximately 15%[1]. However, the risk of colectomy within 5 years of diagnosis has not changed significantly over the past 20 years raising a question about the efficacy of contemporary medical management in altering the overall risk of colectomy in the first 5 years of diagnosis, particularly amongst patients with an early onset severe disease phenotype.

It is thus important to try and gauge the impact of both thiopurines and aTNF in long-term surgical outcomes. Table 1 summarises the key literature with regards to both thiopurines and aTNF and their impact on surgical outcomes.

Thiopurines and long-term surgical outcomes

Data from randomised clinical trials addressing risk of surgery and efficacy of thiopurines is limited. Early trials reported conflicting results, but were limited by small patient numbers[4,11].

A recent Cochrane review comparing AZA or 6MP *vs* placebo or best treatment in patients with UC included only 6 randomised controlled trials (RCT). Although the review strongly favoured AZA use for achieving clinical remission, long-term colectomy was not considered as a measured endpoint[12].

A number of large population based studies have attempted to quantify the impact of immuno-modulators on surgery in UC, with more encouraging findings. Kaplan *et al*[13] reported a population time trends analysis on colectomy rates in a Canadian cohort of UC patients between 1997 and 2009. Over the study period, there was a clear reduction in elective colectomy rates by 7.4% per year, but rates for emergency procedures remained static. Over the same period, the authors reported a doubling of thiopurine usage but were cautious about making inferences about any trend given the absence of a clear inflection point between increased immuno-modulator use and reduced colectomy rates. In a large Canadian population based study from Manitoba including 3752 UC patients with up to 25 years of follow up, a colectomy rate of 10.4% at 10 years was reported[14]. Almost quarter of the cohort exposed to immuno-modulator had undergone colectomy by 5 years. In a sub-analysis of thiopurine users, patients exposed to more than 16 wk of therapy had a significantly decreased colectomy rate at 2 years (5.6% *vs* 12.8%), although immuno-modulator use was not included in the final logistic regression analysis calculating risk of early or late colectomy. Similarly, a large Danish registry study of IBD patients showed a reduction in colectomy rates in patients with UC over the 32 year study period. This decrease was in parallel with a significant increase in thiopurine use, although regression analysis did not indicate a significant protective effect of thiopurine exposure on colectomy[10].

The potential value of prolonged thiopurine exposure was further evaluated by Chhaya *et al*[15] in a United Kingdom population based cohort study of 8673 patients with UC between 1989 and 2009. After adjusting for confounding factors, the authors found no significant fall in colectomy rates within 5 years of diagnosis during the

Table 1 Summary of key research investigating impact of thiopurines and tumour necrosis factor inhibitors therapy on long-term surgical outcomes in ulcerative colitis

	Ref.	Study design	Population	*n*	Key findings
Thiopurines	Ardizzone *et al*[11]	RCT comparing AZA *vs* 5-ASA	Steroid dependent UC	72	No difference in colectomy rates at 6 mo between AZA and 5-ASA groups
	Kaplan *et al*[13]	Population based time trends analysis of colectomy rates	Unselected UC	N/A	Reduction in elective colectomy rates of 7.4% per year Doubling of TP use over the study period Emergency colectomy rates remain static
	Targownik *et al*[14]	Population based analysis of colectomy rates	Unselected UC	3752	10.4% colectomy rate at 10 yr post diagnosis > 16 wk TP therapy associated with reduced colectomy requirement
	Chhaya *et al*[15]	Population based time trends analysis of colectomy rates	Unselected UC	8673	TP use > 12 mo associated with a 71% reduction in risk of colectomy Early TP use not associated with added benefit No significant change in colectomy rates over study period
	Cañas-Ventura *et al*[16]	Retrospective descriptive cohort study of UC patients receiving AZA	Unselected UC	1334	5 yr colectomy rate at 8.8% TP use within 33 mo of diagnosis associated with increased risk of colectomy
aTNF	Sjöberg *et al*[24]	Multi-centre retrospective analysis of IFX rescue therapy	Acute severe UC	211	64%, 59% and 53% colectomy-free survival at years 1, 3, 5 Majority of colectomies within first 2 wk of IFX therapy
	Gustavsson *et al*[26]	RCT comparing IFX rescue therapy *vs* placebo	Acute severe UC	45	3 yr colectomy free survival 50%
	Laharie *et al*[29]	Head to head RCT comparing IFX *vs* CSA as rescue therapy	Acute severe UC	115	No significant differences in colectomy rates between two therapies at 3 mo
	Sandborn *et al*[19]	ACT 1 and 2 RCT of IFX *vs* placebo	Moderate to severe UC	728	Colectomy rate significantly lower in IFX group (10% *vs* 17%) at 54 wk
	Feagan *et al*[41]	ULTRA 1 and 2 RCT of ADA *vs* placebo	Moderate to severe UC	963	Very low colectomy rates reported at 52 wk (approximately 4%) No difference in colectomy rates between ADA and placebo
	Reich *et al*[45]	Time trends analysis of colectomy rates following introduction of IFX	Unselected UC	481	19% annual decrease in elective colectomy in biologic era 15% annual decrease in emergency colectomy in biologic era
	Costa *et al*[50]	Meta-analysis of aTNF use in UC	Moderate to severe UC	836	Reduced risk of surgery at 1 yr in patient treated with IFX compared to placebo (OR = 0.55) NNT was 11

UC: Ulcerative colitis; aTNF: Tumour necrosis factor inhibitors; RCT: Randomised controlled trial; AZA: Azathioprine; TP: Thiopurine; 5-ASA: 5-aminosalicylic acid; IFX: Infliximab; CSA: Ciclosporin; ADA: Adalimumab; NNT: Number needed to treat; N/A: Not applicable; ACT: Active ulcerative colitis trials; ULTRA: Ulcerative colitis long-term remission and maintenance with adalimumab.

20 year study period. Also, requirement for thiopurines defined a group of patients with an associated higher risk of colectomy[15]. Amongst patients treated with thiopurines, use for greater than 12 mo (compared to use ⩽ 3 mo) was associated with a significant reduction in requirement for colectomy by end of follow up (HR = 0.29, 95%CI: 0.21-0.40). But, early thiopurine use (defined as within 1 year of diagnosis of UC) added no additional reduction suggesting some patients with early onset severe disease were either refractory to thiopurines or had insufficient time to benefit from these drugs before surgery was required.

Most recently, Cañas-Ventura *et al*[16] described colectomy rates and risk factors for colectomy in a cohort of 1334 Spanish UC patients drawn from a national IBD registry. All patients had had a minimum exposure to immuno-modulator therapy (AZA at median dose of 150 mg/d or 6-mercaptopurine at a median dose of 75 mg/d) of at least 3 mo. The 5 years cumulative risk of colectomy for the cohort was 8.8%, and regression analysis demonstrated an increased risk of colectomy in patients receiving immuno-modulator therapy within the first 33 mo of diagnosis *vs* those started after this time (HR = 4.9, 95%CI: 3.2-7.8).

Data from "real world" single centre retrospective studies are limited and conflicting in their reporting of the effect of thiopurine therapy on surgery. Williet *et al*[17] reported medication usage in 151 unselected UC patients (median follow up 58 mo) and their subsequent risk of needing colectomy. In this study, exposure to thiopurine therapy was not associated with an increased risk of colectomy risk in regression analysis. In contrast, data from a Japanese single centre study of 222 UC patients followed for up to 11 years indicated a significant protective effect of thiopurine treatment on colectomy (HR = 0.2, 95%CI: 0.08-0.67), although the sub-analysis only included hospitalised patients[18].

In summary, there is limited data from prospective controlled trials and retrospective observational studies to support a protective effect of thiopurine therapy in reducing the overall risk of colectomy. This is inherently related to the design of most studies that focus on non-

surgical short-term measures as primary outcomes. Longitudinal population based data is possibly more supportive of the protective role of thiopurine therapy against colectomy, and sufficient exposures may be required to reduce this risk, but this might not be always possible in patients with an early onset severe disease phenotype.

aTNF therapy and long-term surgical outcomes

The Active Ulcerative Colitis Trials (ACT 1 and ACT 2) published in 2005 by Rutgeerts *et al*[8] showed the potential benefit *vs* placebo of the aTNF agent, infliximab (IFX), on clinical and endoscopic responses in 728 outpatients with moderate-to-severe UC. Colectomy data from this cohort was later reported in 2009[19]. The analysis indicated a cumulative incidence of colectomy of 10% in the IFX group compared to 17% in the placebo group (HR of 0.59, 95%CI: 0.38-0.91) pointing to a protective effect against colectomy. However, the median follow up was only 6.2 mo and there was a significant study drop-out rate, nor was the indication for colectomy clearly defined. In contrast, a placebo-controlled study by Järnerot *et al*[20] in 2005 looking at IFX therapy in 45 patients with fulminant UC reported a 29% colectomy rate in the treated arm at the end of the trial (90 d) *vs* 67% in the placebo arm[20]. The wide discrepancy in colectomy rates between the 2 studies reflects differing patient subtypes enrolled in both trials, namely chronic non-acute severe cases *vs* acute severe colitis patients, and this is considered further below.

Acute severe UC: Several small retrospective single centre observational studies exist recording colectomy rates following aTNF treatment in acute severe UC[21-23]. Colectomy was required in 37%-53% of patients, although there was considerable heterogeneity in the patient subgroups and follow up periods (6-22 mo) between the different studies. A large Swedish multi-centre retrospective analysis of 211 aTNF-naive patients with acute severe UC treated with 5 mg/kg IFX as "rescue" therapy reported colectomy free survivals of 64%, 59% and 53% at years 1, 3 and 5 suggesting a considerable long term protection against colectomy in this group of patients[24]. However, in this study 64% of all the colectomies (*i.e.*, IFX failures) in the first year occurred within the first 2 wk possibly suggesting a sub group of patients with more severe disease in whom IFX cannot alter risk of colectomy. More recently, accelerated aTNF induction regimes have been shown to reduce very early colectomy in acute severe UC, although long-term colectomy free survival does not appear to be improved with this strategy[25].

Gustavsson *et al*[26] prospectively reported similar 3 years colectomy-free survival rates of 50% in the treated arm of the original 45 patients with acute severe UC entered into an earlier RCT by Järnerot *et al*[20], although some patients had further IFX rescue treatments in follow up and there were differing rates of immuno-modulator use in the treatment and placebo arms, making interpretation of this study difficult[26]. Of particular note, mucosal healing at 3 mo was strongly inversely related to the need for colectomy, with a colectomy rate of 0% in those who achieved mucosal healing at 3 mo, compared to 50% in patient who did not. The importance of achieving mucosal healing with respect to reducing the need for colectomy in UC patients treated with IFX has been further highlighted in a number of other studies including a sub-analysis of the original ACT trials[27,28].

The available evidence suggests a protective effect of aTNFs in reducing colectomy rates in patients with acute severe UC in the short-term. However, this effect does not appear to be superior to "rescue" therapy with ciclosporin. The results of the CYSIF trial, a randomised open labelled trial comparing ciclosporin *vs* IFX in 115 patients with acute severe UC (who failed to respond to 5 d of intravenous corticosteroid therapy), showed no significant differences in colectomy free survival at 98 d in either group (25.9% *vs* 26.3% respectively)[29]. In contrast, results from the United Kingdom national IBD audit indicated a significantly higher emergency colectomy rate in acute severe UC patients "rescued" with ciclosporin compared to IFX (35% *vs* 19%), although only colectomies performed in the same index admission were considered and may reflect selection bias[30]. Meta-analyses on this subject have not established superiority of either therapy in the context of acute severe UC[31,32]. Moreover, Laharie *et al*[33] has recently presented (in abstract) the long-term follow up data from the original CYSIF trial participants that indicates no significant differences in long-term colectomy-free survival between ciclosporin and IFX (5 years colectomy-free survival 61% ± 7% in ciclosporin group *vs* 65% ± 7% in IFX group)[33]. The full analysis is awaited, along with the findings of CONSTRUCT, a United Kingdom based trial on the same topic[34].

Moderate to severe UC: The term moderate-to-severe UC includes a heterogenous population of colitic patients including steroid-dependent UC and steroid-refractory UC, making comparison of studies more difficult.

Following the ACT 1 and ACT 2 trials, a number of smaller uncontrolled single centre retrospective observational studies on the effect of aTNF therapy on colectomy rates beyond 6 mo have been published[35-38]. All had follow up periods of at least 12 mo. In these "real life" descriptions of aTNF use, there was considerable variation in the colectomy rates, from 2.7% at 42 mo to 53.3% at 12 mo. However, patient numbers in these studies were limited and there was significant disparity in patient demographics, disease extent, and severity. Reinisch *et al*[39] published the results of the extension study from the original ACT trials in 2012. Patients who had achieved benefit from IFX in ACT 1/2, were offered a further 3 years of treatment. Those on 5 mg/kg doses had the option to increase the dose to 10 mg/kg if the investigators felt response had been lost. From 229

patients accepted into the 3 year extension study, there were only 2 colectomies (< 1%). This result should be treated with caution regarding the long-term benefits of aTNF therapy since it can be argued that those patients who survived without colectomy beyond the early stages of diagnosis have inherently less aggressive disease. Secondly, by virtue of their early response in ACT 1 and 2, these patients may have more responsive disease. Additionally, up to half of the original ACT 1 and 2 patients in the treatment arm were also on immuno-modulator therapy, which may have provided additional benefit in reducing the need for colectomy.

The ULTRA 1 and ULTRA 2 trials were randomised placebo controlled trials of Adalimumab (ADA) for the induction and maintenance of remission in moderate to severe UC[9,40]. In 2014, Feagan *et al*[41] published the hospitalisation and surgical outcomes from this cohort. Interestingly, no differences in the colectomy rates between treatment and placebo arm during the 52 wk follow up was found. However, overall reported colectomy rates were only 4%-5%, and the authors acknowledged that this surprisingly low rate meant the study was insufficiently powered to assess for differences in surgical outcomes. Again there was a large proportion of patients on concomitant immuno-modulator therapy in both treatment and placebo arms (37% *vs* 35%). In a subsequent meta-analysis of 5 RCTs comparing ADA or IFX against placebo (including both ACT and ULTRA trials), both were equally efficacious in achieving clinical remission at 52 wk compared to placebo, but unfortunately no colectomy data was considered in the comparison[42].

In a retrospective study of 48 Spanish ENEIDA registry patients with either steroid dependent UC or steroid refractory UC treated with ADA, colectomy rates were reported at 22.9% after a mean of 205 d[43]. Clinical response was determined using the Mayo/partial Mayo scores at week 12, 28 and 54. The only predictor of colectomy was failure to respond to ADA at week 12. However, it was noted by the researchers that there was a high variation of co-medication with other IBD drugs, and that 81% of the cohort had already tried IFX prior to their induction with ADA.

A number of researchers have attempted to determine whether the use of aTNF therapies may alter surgical outcomes using epidemiological methods. Cannom *et al*[44] used United States Nationwide Inpatient Sample data combined with census data to estimate surgical rates in the 7 years following the Food and Drug Administration approval for IFX in IBD. No downward trend in surgery was seen over the study period of 1998-2005 in either Crohn's disease or UC, but arguably it was too early to see a noticeable effect of IFX on surgical rates over this relatively short period. Reich *et al*[45] performed a time-trends study of colectomy incidence rates in a Canadian subpopulation of UC patients before and after the approval of IFX for UC treatment in 2005. In the biologic era, the annual percentage of both emergency and elective colectomy rates fell: 18.6% (95%CI: 13.8%-23.3%) and 14.9% (95%CI: 2.18%-25.8%) respectively. This occurred during a period of rapid increase in the proportion of IFX use and no proportional changes in the use of other IBD medications. A relationship between the two was inferred, but the authors accept there may have been other changes in management that could have contributed to declining colectomy rates over this time. Most recently, preliminary data from a very large United States cohort of almost 400000 UC patients admitted to hospital between 1998 and 2011 showed no change in colectomy rates in the era before and after the introduction of aTNF[46].

Meta-analyses on the subject have helped clarify the clinical question. Recently, Lopez *et al*[47] performed a meta-analysis of 5 placebo controlled RCTs[8,9,40,48,49] assessing efficacy of a variety of aTNF therapies including IFX, ADA and Golimumab in patients with moderate to severe UC. The authors concluded that treatment with aTNF was superior to placebo in achieving the primary endpoints (maintaining remission and achieving mucosal healing), but only IFX had any effect on reducing colectomy rates. However, only 2 studies[19,41] were included in the analysis of surgery. In overall analysis of both studies, aTNF therapy was not more effective than placebo in reducing the risk of colectomy (RR = 0.87, 95%CI: 0.42-1.81). In subgroup analysis, IFX was superior to placebo in reducing the need for colectomy (RR = 0.64, 95%CI: 0.43-0.97) although follow up was limited to only 6.2 mo. A similar protective effect was not seen for ADA.

An earlier systematic review and meta-analysis of 27 IBD studies was published in 2013 by Costa *et al*[50], and included data for 836 UC patients treated with IFX only. Pooled results from 4 RCTs with follow up ranging from 6 to 156 wk (including 3 studies not assessed in the meta-analysis by Lopez) suggested a reduced risk of surgery with IFX (pooled OR = 0.55, 95%CI: 0.40-0.76, number needed to treat = 11)[19,26,51,52]. However, the analysis was very heavily dependent on the findings from ACT 1 and 2 follow up (91% weighted), and furthermore, a similar protection against colectomy was not seen in the pooled data from the observational studies (although there was considerable heterogeneity in these studies).

In summary, whilst there appears to be a clear benefit of aTNF in inducing clinical remission and achieving mucosal healing in UC patients in the short term, whether this is translated to long-term reduction in surgical risk is less apparent, and data is lacking. Available studies are limited, follow up is short, and patient populations are heterogenous. Similarly, population based studies are also conflicted regarding the role of aTNF therapy in altering the long-term risk of colectomy. No data is available regarding the long term benefits of Golimumab in this respect.

Physicians must also consider the potential detrimental side of aTNF use in this patient group, notably the possible impact of these medications on post-

Table 2 Summary of key research investigating impact of thiopurines and tumour necrosis factor inhibitors therapy on hospitalisation in ulcerative colitis

	Ref.	Study design	Population	*n*	Key findings
Thiopurines	Actis *et al*[61]	Retrospective study comparing hospitalisation before and after AZA induction	Severe UC	17	Significant decrease in hospitalisation for patients with UC up to 5.8 yr following AZA induction Most of patients were also treated with ciclosporin at AZA induction
	Herrinton *et al*[62]	Population based cohort study of prescribing trends in UC	Unselected UC	5895	150% increase in immuno-modulator use in UC between 1998-2005 Concurrent reduction in UC hospitalisations in the same period by a third
	Vester-Andersen *et al*[63]	Prospective descriptive study of IBD inception cohort	Unselected UC	300	26% exposure to immuno-modulator during follow up Hospitalisation rates decreased from 4.7 d/person-years in year 1 after diagnosis to 0.4 d in year 5 Immuno-modulator therapy found not to be significant in predicting need for hospitalisation
aTNF	Carter *et al*[65]	Medical insurance cost analysis study	Unselected UC	420	UC patients with a prescription for infliximab for > 80% of the study period had less hospitalisation requirement, lower admission costs and shorter inpatient stays
	Oussalah *et al*[37]	Multicentre retrospective study on outcomes in UC patients post aTNF	Unselected UC	191	Estimated hospitalisation-free survival at 1, 2, 3 and 6 yr were 66.7%, 60.2%, 57.1% and 44.6% respectively Earlier use of aTNF predictive of need for hospitalisation
	Sandborn *et al*[19]	ACT 1 and 2 RCT comparing IFX with placebo	Moderate to severe UC	728	Of patients treated with IFX, 84% remained free of hospitalisation at 54 wk, compared to 75% in the placebo group
	Feagan *et al*[41]	ULTRA 1 and 2 RCT comparing ADA with placebo	Moderate to severe UC	963	Significantly reduced all-cause and UC-related admissions at both 8 wk and 52 wk in patients treated with ADA compared to placebo
	Lopez *et al*[47]	Meta-analysis of aTNF in UC outcomes	Moderate to severe UC	964	aTNF therapy was superior to placebo in reducing UC-related hospitalisations, with a relative risk of 0.71 (95%CI: 0.56-0.90)

UC: Ulcerative colitis; aTNF: Tumour necrosis factor inhibitors; RCT: Randomised controlled tria; AZA: Azathioprine; IFX: Infliximab; ADA: Adalimumab; IBD: Inflammatory bowel disease; ACT: Active ulcerative colitis trials; ULTRA: Ulcerative colitis long-term remission and maintenance with adalimumab.

operative complications and/or mortality. In a large study by Ellis *et al*[53], post-colectomy mortality rates increased significantly between the era before and after the introduction of aTNF use in UC. A recent systematic review suggested increased post-operative complications in patients with Crohn's disease on aTNF therapy[54]. However, data from other smaller UC cohorts have not indicated similar findings in patients treated with these agents[55].

Clearly, further work into the long-term protective role of aTNF drugs is required. Equally, the additional benefit of co-administration of TPs with aTNF therapy remains largely unexplored. Recent studies addressing this have not shown any additional protection against colectomy, but this strategy warrants further investigation in the future[56].

HOSPITALISATION

The overall rate of hospitalisation in UC appears to be decreasing. Data from recent population based longitudinal studies indicate a declining trend in UC related admissions[57,58], although this is not universally reported in all populations[59,60]. A variety of environmental, demographic and clinical parameters have been implicated as potential risk factors for hospitalisation in patients with UC, although studies into the impact of specific medications on this outcomes are limited. Table 2 summarises the key research in this area.

Thiopurines and hospitalisation

Data regarding the impact of thiopurine use on the risk of hospitalisation is limited. A small retrospective study of 17 patients with severe UC assessed the frequency of admission to hospital before and after the initiation of AZA[61]. Analysis showed a significant decrease in the number of hospital admissions from a mean of 2.12 ± 0.69 in the preceding 4.2 ± 4.3 years to a mean of 0.12 ± 0.33 in the following 5.8 ± 2.5 years ($P = 0.000$) after initiation of AZA. However, numbers were very small, and 14 of the subjects were also treated with ciclosporin to achieve remission at the time of induction with AZA. A large study from the United States Kaiser Permanente healthcare database between 1998-2005 reported trends in medication use and a variety of key outcomes in a cohort of 5895 UC patients[62]. Over the study period, immuno-modulator therapy in UC patients increased by 150% (steroid and 5-aminosalicylic acid use also increased over this period but to a much less extent). Over the same period acute hospital admissions were reduced by almost a third. A relationship between these two findings can only be made by inference. However, as the study was performed in an era before United States approval of aTNF agents in UC, there is no confounding by this medication group.

Most recently, Vester-Andersen *et al*[63] published the hospitalisation rates of a Danish inception cohort of IBD patients including (300 patients with UC) between 2003 and 2011. Forty-seven percent of the UC cohort

had at least one admission to hospital over the follow up period, and admission rates decreased from 4.7 d/person-years in year 1 after diagnosis to 0.4 d in year 5. Twenty six percent of UC had exposure to immuno-modulator therapy in follow up with a median time to exposure of 433 d from diagnosis. In a sub-analysis, however, immuno-modulator exposure was not found to be significant in predicting the need for hospitalisation.

In summary, data is lacking to suggest with certainty that immuno-modulator therapy has a role in avoiding hospitalisation in UC.

aTNF therapy and hospitalisation

The cost of biologic therapy has dramatically shifted the overall healthcare costs in IBD. The recent Dutch COIN study sought to estimate the expenditure of medications, treatments and hospitalisation of large cohort of adult IBD patients including 937 UC patients[64]. The biggest cost driver was medication, notably aTNFs, with hospitalization and surgery accounting for 19% and < 1% respectively of total costs. Hospitalisation remains costly for healthcare providers, and if medical therapy can reduce the need for admission, this can potentially offset the cost of expensive treatments.

Relatively few retrospective observational studies have looked at hospitalisation rates with respect to aTNF use in UC. Carter *et al*[65] published the results of a cost analysis based on 420 UC patients' medical insurance claims for IFX treatment in relation to hospitalisation and admission costs. In a sub-analysis whereby patients were categorised by persistent IFX use (defined as having a prescription of IFX > 80% of the time), patients with "persistent" maintenance therapy had less hospitalisation (3% *vs* 20.4%), lower inpatient costs, and shorter inpatient stays.

In a French multi-centre retrospective analysis of 191 unselected UC patients with varied severity treated with IFX, 36.1% of patients required at least one admission during follow up[37]. Estimated hospitalisation-free survival at 1, 2, 3 and 6 years were 66.7%, 60.2%, 57.1% and 44.6% respectively. Earlier time from diagnosis to IFX treatment was strongly predictive of need for first hospitalisation. Conversely, a small study from Hungary showed no change in hospitalisation rates in UC patients following the introduction of IFX treatment compared to the pre-IFX era[66].

A follow up study to ACT 1 and 2 also examined hospitalisation rates[19]. In the treatment arm, 84% remained free of hospitalisation at 54 wk, compared to 75% in the placebo group. The proportion of patients requiring 1, 2 or more than 2 UC-related admissions was also significantly higher in the placebo group. Similarly, findings from ULTRA study also reported significantly reduced all-cause and UC-related admissions at both 8 wk and 52 wk in patients treated with ADA compared to placebo[41].

Two meta-analyses have evaluated the impact of aTNFs on rates of hospitalisation[49,50]. A sub-analysis of hospitalisation by Lopez *et al*[49], included 964 UC patients receiving aTNF derived from two RCTs with follow up between 52 and 54 wk. aTNF therapy was superior to placebo in reducing UC-related hospitalisations, with a relative risk of 0.71 (95%CI: 0.56-0.90). In a separate analysis, both IFX and ADA were found to be effective in reducing UC-related hospitalisations, with a number needed to treat of 18 (95%CI: 9-911) and 23 (95%CI: 12-506) respectively. Costa *et al*[50] also found a 49% (OR 0.41, 95%CI: 0.40-0.65) reduction in risk of hospitalisation in UC patients treated with IFX compared to placebo in analysis of three RCTs not included in the study by Lopes.

In summary, aTNF agents appear to have a potential effect in reducing hospitalisation in patients with UC. Most research on hospitalisation focuses on early admission rates (under a year). There is clear need to further evaluate the impact of these medications on hospitalisation in the longer term.

CONCLUSION

Thiopurines and aTNF therapy form a key part of treatment in patients with UC. Both have established roles in the induction and maintenance of remission. Their role in altering the long-term requirement of surgery and hospitalisation is less clear. Whilst 5 years surgery rates have reduced in Crohn's disease, they remain essentially unchanged in UC[1]. Thiopurines appear to have a long-term benefit in reducing the need for surgery in UC, although there is a subgroup of UC patients who do not derive benefit from these medications, and require early colectomy. Whereas IFX reduces the need for surgery in the short-term, the evidence that aTNF agents alter the long-term requirement of colectomy is again limited.

The role of thiopuriness and aTNFs in reducing hospitalisation is more difficult to interpret in the context of differing models of healthcare provision and changes in other aspects of UC management. However, overall the evidence generally supports their respective roles in reducing acute admissions. Further work is required to evaluate the important question of the long-term benefits of medical therapy on reducing the requirement of for surgery and hospitalisation in UC.

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