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Immunomodulators: friends or enemies in surgery for Crohn's disease?

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Abstract

Crohn's disease is characterized by discontinuous transmural inflammation involving any portion of the gastrointestinal tract and may have a severe impact on quality of life. As it is a chronic disease it needs surgery and medicine as complementary therapies aimed at maintenance of remission and to prevent relapsing of symptoms and need of further surgery. Surgery in Crohn's disease is often performed in patients with a number of well-known risk factors of post-operative complications, especially intra-abdominal septic complications. This review will look at the current knowledge of immunomodulating therapies in the peri-operative phase of Crohn's disease. The effect of immunomodulators in regards of post-operative complications is evaluated in clinical reports and compared with data from animal studies and the influence on wound healing. Further, the effect of immunomodulators on preventing, or at least postponing, primary as well as repeat surgery in Crohn's disease is reviewed in general or in selected high risk cohorts as well as the timing thereof.

Abbreviations

Anti-TNF	Anti-Tumor Necrosis Factor
Aza	Azathioprine
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	Confidence Interval

DSS	Dextran Sulfate Sodium
IBD	Inflammatory Bowel Disease
ICAM-1	Inter Cellular Adhesion Molecule-1
OR	Odds Ratio
RCT	Randomized Controlled Trial
TGF- β	Transforming Growth Factor β
TNBS	Trinitrobenzensulfonic acid
UC	Ulcerative Colitis
5-ASA	5-Aminosalicylic acid
6-MP	6-Mercaptopurine

Introduction

Crohn's disease (CD) is an inflammatory bowel disease (IBD) and characterized by discontinuous transmural inflammation involving any portion of the gastrointestinal tract, with the ileum and colon most commonly affected^{1 2}. Symptoms are dominated by abdominal pain and obstructions but diarrhoea and mucous in the stool, as well as fistulas, are quite frequent³⁻⁵. CD is sometimes associated with extra intestinal manifestations like arthralgia, eye, skin and liver manifestations like primary sclerosing cholangitis^{3 6}. There is quite often a time lag between symptoms and diagnosis in CD and some have had symptoms for many years before the diagnosis is finally established⁷. There is as yet no gold standard diagnostics of CD⁸ which remains a test of clinical skill depending on relevant patient history, attentive physical examination, judicious laboratory testing, and detailed review of radiographic, endoscopic, and pathologic data⁸.

The disease was first treated with extensive resection⁹, with the inherent risk of developing short bowel syndrome and intestinal failure^{10 11}. The extent of surgical resection has since repeatedly been shown to be of less importance for treatment outcome¹²⁻¹⁴, and today bowel-preserving techniques are preferred and where inflamed areas are often not surgically removed and short strictures may be treated by strictureplasty instead of resection¹⁵⁻¹⁸.

As CD is a chronic disease with no definite cure it may have a severe impact on quality of life compared with the general population due to lack of energy, pain, diarrhea, malnutrition, perianal disease, ostomy-related concerns and the uncertain nature of disease in general¹⁹⁻²¹. Previous studies have shown that such impairment in quality of life is associated with disease activity rather than the disease itself or even the localization or behavior of the disease^{20 22-27}. The different therapies for CD are focused on relief of symptoms and dealing with complications to the disease. In active disease, induction of remission can be achieved either through medical therapy or surgery. When patients have no or limited symptoms therapies are aimed at maintenance of remission and to prevent relapsing of symptoms and need of further surgery. It is important to remember that most patients spend most of their life in remission²⁸ and that medical therapy and surgery used as *complementary* therapies can achieve remission with low symptomatic load in many patients^{29 30}. The correlation

between remission and quality of life is strong, regardless if remission was achieved medically or surgically^{31 32}.

Immunomodulators

Thiopurines are anti-metabolites developed during the 1950's and consists of three different drugs, 6-mercaptopurine (6-MP), azathioprine (Aza), and 6-thioguanine. They were first introduced as chemotherapy for cancer but today they are widely used as immunomodulators after transplantation as well as treatment of inflammatory bowel disease³³⁻³⁷. In Crohn's disease thiopurines are used to treat active disease in the hope of inducing remission and may thereafter be used to maintain remission. They are also used as prophylaxis against disease progress either upfront or following surgery in order to prevent recurrence.

Azathioprine has been endoscopically shown to heal the mucosa of both ileitis and colitis in Crohn's disease^{38 39}. The place of thiopurines as maintenance therapy in IBD is well established^{35 36} why they have been increasingly used over the years^{40 41}. Healing of mucosal lesions within one year after initiation of medical therapy have been found to predict a favourable five year outcome concerning the degree of inflammation, need for repeat steroids and resectional surgery⁴². A Cochrane review showed a number needed to treat of six for quiescent disease but also a steroid sparing effect with a number needed to treat of three³⁷. The results of a study by Markowitz *et al* on children with newly diagnosed Crohn's disease were in favour of starting thiopurines earlier in the course of the disease⁴³. There are several ongoing studies to verify this finding in adults as well⁴⁴. A French study found a high relapsing risk of Crohn's disease if the thiopurine therapy was interrupted, thus suggesting the thiopurine therapy not to be withdrawn if once tolerated⁴⁵.

However, approximately 15% of patients have to end their thiopurine therapy because of negative side effects⁴⁶. Both 6-MP and Aza are pro-drugs that are activated in the body through extensive metabolism⁴⁷. Measurements of thioguanine nucleotides have been attempted to monitor the use of thiopurines and find the optimal dosage but with limited value⁴⁶. There is however data in favour of phenotyping and/or genotyping the catabolic enzyme thiopurine S-methyltransferase (currently 23 genetic variants have been described)

prior to thiopurine therapy is commenced in IBD to prevent severe haematotoxicity⁴⁸⁻⁵⁰. All intolerance is not dose-dependent and it seems that some patients not tolerating Aza do tolerate a switch to 6-MP or 6-thioguanine^{46 51}.

Other immunomodulators used with variable success in CD including methotrexate, mycophenolate mofetil, tacrolimus, and cyclosporine A⁵²⁻⁶², but are so far regarded as a third line therapies in patients intolerant to thiopurines⁶³⁻⁶⁵.

The risk for post-operative complications in CD appears to be increased compared with colorectal surgery in general⁶⁶⁻⁶⁸. At least some of this risk increment owes to the fact that surgery in CD by necessity often is performed in patients with a number of well-known risk factors such as previous surgery, preoperative malnutrition, intra-abdominal abscesses or fistulas, bowel obstruction, steroid treatment, and possibly immunomodulation⁶⁹⁻⁷⁴. A negative dose-response effect from preoperative steroid treatment on anastomotic complications is well established from a number of studies and in meta-analyses^{69-73 75 76}. Poor nutritional status or low preoperative serum albumin have been found in earlier reports to be risk factors for intra-abdominal septic complications^{69 71} together with anemia⁷⁷ and emergency surgery⁷⁸. Unsurprisingly, one of the factors most convincingly associated with post-operative intra-abdominal septic complications in up to 25% is presence of preoperative intra-abdominal abscess or fistula^{69-71 74 79-83}. The risk for anastomotic complications has also been shown to increase with the number of identified preoperative risk factors raising from below 5% in CD patients without any identified risk factor, to 14-30% with one risk factor, 16-38% with two risk factors, and as high as 26-100% with three or four risk factors present^{69 71 74 79}.

Surgeons have long been concerned that immunomodulation with e.g. thiopurines may impair healing and could be another risk factor for anastomotic complications^{74 84}, through mechanisms of impaired healing of the anastomosis and wound. The potential effect by immunomodulators on the healing capacity after surgery could be multi-factorial, suggested mechanisms include decreased proliferation and increased apoptosis of epithelial cell as well as T-cell-mediated suppression of the inflammatory reaction leading to reduced collagen synthesis and wound strength^{85 86}. The knowledge in this respect is however rather limited. Clinical reports on the use of immunomodulators in relation to surgery are often

focused on postoperative septic complications in general and do not always distinguish between CD and ulcerative colitis (UC) patients^{72 87 88}.

This review will try to shed some light on the current knowledge of immunomodulators, with a focus on thiopurines, and their role in the peri-operative phase. Both advantages and disadvantages in the pre- and post-operative setting will be discussed.

Medication prior to surgery

Immunomodulators effect on postponing primary surgery

A key question when it comes to immunomodulators is whether they are able to slow down disease progression in CD and thereby reduce the need of hospitalizations and the risk of surgery⁸⁹⁻⁹¹.

In children and young adults (n=1,595) the risk for surgery among CD patients with thiopurine use (n=787) was 15.3% after 5 years in comparison with 22.1% in those without thiopurines (n=808) (log-rank p=0.02)⁹². During the follow up of in mean 4.3 years the adjusted risk was higher among those on thiopurines (HR 1.85, 95% CI: 1.37-2.50), but when comparing those with early use of thiopurines (within the first year of diagnosis) there was a risk reduction compared with patients starting thiopurines later than one year of CD diagnosis (HR 0.61, 95% CI: 0.41-0.91).

In Australia Kariyawasam *et al* studied the use and effects of thiopurines, and to some extent methotrexate (16% of those on immunomodulating therapy), in 1,035 CD patients at a tertiary referral center from 1970 to 2009⁹³. The use of thiopurines increased from 12.0% to 54.3% over time (p<0.0001) and the use within the first year increased from 1.3% to 35.8% (p<0.0001). Immunomodulators started within the first three years of diagnosis was associated with a lower risk of first abdominal surgery (HR 0.45, 95% CI: 0.32-0.63) or perianal surgery (HR 0.30, 95% CI: 0.16-0.56)⁹³ in multivariable analysis. A similar pattern was seen in 506 incident CD patients from Hungary where the 1- and 5-year probability of thiopurine use increased from 3.2% and 6.2% to 34.8% and 46.2% between 1977 and 2008⁹⁴. Using the same definition of early use as the Australian report, they found a lower

risk of first intestinal surgery in patients with early immunomodulation compared to patients without thiopurines within the first three years (HR 0.43, 95% CI: 0.28-0.65)⁹⁴.

An English study including 5,640 CD patients by Chatu *et al* showed that the 5-year probability of being treated with thiopurines increased from 12% to 25% during the time period 1989-2005 ($p < 0.0001$)⁹⁵. The 5-year risk of first intestinal resection in the same report was 7% in patients with >12 months of thiopurine use compared with 12% in those without or <12 months of thiopurines ($p < 0.001$), and in a Cox regression analysis giving a HR 0.31 (95% CI: 0.22-0.22) while early treatment (within the first year) had a comparable impact as late initiation of thiopurines⁹⁵. Similar findings were reported from Cardiff by Ramadas *et al*, who found a significant increase in the use of early thiopurines (within first year of diagnosis), ranging from 3% in 1986-1991 to 25% in 1998-2003⁹⁶ coinciding with less CD related surgery, decreasing from 59% to 25% after five years for the same time periods and with a multivariable Cox regression thiopurines within the first year of diagnosis found a HR 0.47 (95% CI: 0.27-0.79)⁹⁶. This was not confirmed by Qiu *et al* who found no signs of effect on disease progression or need for surgery in patients with early thiopurine therapy in comparison with conventional management⁹⁷. The same group found a greater chance of long term (after 36 months) endoscopic remission in patients on thiopurines with an endoscopic response after 12 months of initiated therapy, but once again no effect regarding need of surgery⁹⁸.

In patients with late onset CD ($n=1,349$) the risk of resectional surgery was not reduced among the 16.4% of patients who started thiopurine treatment during follow up. The time from diagnosis to start of thiopurines was 18.2 months and no effect was seen regardless if thiopurines were used for more or less than 12 months (mean duration of 33.9 months)⁹⁹.

A French open label randomized controlled trial (RCT) on early use of thiopurines (within six months of CD diagnosis) found a lower risk of perianal surgery after 3 years; 3% in the active group compared with 13% in the control group ($p=0.04$)¹⁰⁰, similar to the finding by Kariyawasam *et al*⁹³. No such effect was found for intestinal surgery (8% vs 6%) although this was difficult to interpret as both temporary stomas and closure thereof were included. Similarly Panes *et al* found no gain from early thiopurine use in newly diagnosed CD in terms

of time in steroid free remission, but this study was under powered for disease progression and CD related surgery¹⁰¹.

A review and meta-analysis covering 12,586 CD patients found a 40% risk reduction of surgery in patients treated with thiopurines (HR 0.59, 95% CI: 0.48-0.73)⁹¹. The authors concluded that thiopurines are associated with a risk reduction of first surgery in CD but it is unclear if this is a true reduction or merely a postponing effect. Nor was it possible to adjust for factors like concomitant use of anti-TNF therapy and dose and timing of thiopurine therapy, in regards of time lag from diagnosis to start of treatment as well as time on thiopurines¹⁰². In a Portuguese study on 736 CD patients thiopurines as mono-therapy, as well as in combination with anti-TNF, were associated with a decreased risk of disease progression, HR 0.15 (95% CI: 0.11-0.20) and HR 0.33 (95% CI: 0.21-0.51) respectively. The authors also found an association between an earlier disease progression with a longer delay to initiation of thiopurine treatment as well as shorter duration of treatment¹⁰³

Interestingly a recent meta-analysis showed a small but significant risk reduction for developing colorectal cancer in IBD patients treated with thiopurines, especially in high risk individuals like long standing disease and extensive colitis¹⁰⁴.

Despite what seems to be some benefit of early thiopurine therapy in CD, some question whether at least in some cases the bowel damage is too advanced already at the time of diagnosis and therefore thiopurines are given too late and maybe not for long enough¹⁰⁵. This may especially be true for ileocaecal CD which carries the highest risk of surgery^{96 106 107}. In recent years two randomized controlled trials have compared medical therapy with surgery in ileocaecal CD^{108 109}. The first trial compared thiopurines with ileocaecal resection¹⁰⁸ and the second infliximab with laparoscopic primary resection¹⁰⁹. Neither found any differences in quality of life during follow up but in the LIR!C-trial an important finding was that more than a third of patients starting infliximab treatment required ileocaecal resection during follow up, while in the same time frame only one in four patients with a primary resection was started on anti-TNF¹⁰⁹.

One major concern with early initiation of immunomodulators or biologics is that by postponing surgery, patients tend to have developed more complex disease at the time of

surgery which may be associated with a risk of more extensive resections and postoperative complications. The latter question is so far unanswered but there are some worrying reports concerning the first questions. An American register study looked at the surgical effects during a time period of increasing use of immunomodulators as well as anti-TNF, 1993-2004¹⁰⁶. Despite lack of data on used medication they found a time trend towards less colonic and rectal resections in CD patients but with no effect on ileocaecal resection and a very worrisome increase by 60% in enteric fistulas from the small bowel ($p=0.04$) from the beginning to the end of the study period¹⁰⁶. An increasing frequency of multiple drugs used prior to surgery between 1992 and 2009 was confirmed in a German study¹¹⁰. During the same time period an increasing percentage of patients came to surgery with clinical deterioration including weight-loss and multiple structures involved in inflammatory masses contributing to more frequent use of stomas yet more intra-abdominal septic complications, ranging from 7% at the beginning to 36% at the end. These changes may not be caused by the more aggressive therapies in themselves but rather the timing of surgery and puts focus on the importance of a very close collaboration between gastroenterologists and colorectal surgeons within the field of CD^{111 112}.

Postoperative complications after preoperative use of immunomodulators

Possible reasons for an impaired anastomotic healing with immunomodulation with thiopurines include T-cell-mediated suppression, decreased proliferation and increased apoptosis of epithelial cells^{85 86}. At the same time thiopurines have a steroid sparing effect¹¹³ and the adverse effect of steroids on wound healing might be of greater importance than a possible adverse effect of immunomodulators like thiopurines^{70-72 79}.

There are a number of reports regarding the effect of thiopurines on postoperative recovery and outcome. Most of them are either on a mixture of IBD patients with UC and CD, with concomitant corticosteroid therapy or complications not separated into anastomotic complications and general infectious complications^{72 87 88 114 115}.

Human data

At our own institution we evaluated the outcome in 343 consecutive operations for CD including a primary anastomosis⁷⁴. Intra-abdominal septic complications occurred in 8% and re-intervention within 30 days was required in 10 % of the operations. Patients pre-operatively treated with thiopurines had an increased risk of postoperative anastomotic complications compared to patients without such treatment (16% vs. 6% ($p=0.044$)). Likewise, the rate of surgical re-intervention was increased from 9% to 20% in patients on thiopurine treatment ($p=0.016$). Other independent risk factors in logistic regression analysis were colo-colonic anastomosis and presence of intra-abdominal fistula/abscess prior to surgery⁷⁰.

Aberra *et al* retrospectively studied 159 patients with UC or CD, with elective abdominal surgery, with or without anastomosis, excluding all patients with pre-operative intra-abdominal septic complications and pyogenic complications of the disease⁷². The rate of major infectious complications was 20% for steroid treated patients, 12 % for thiopurines with ($n=34$) or without ($n=18$) steroids, and 4 % for those without any of these treatments ($n=51$). Although the difference was not statistically significant, the rates are similar to our own report⁷⁹. However, the complications were analyzed according to minor (urinary tract infection and temperature $>38.6^{\circ}\text{C}$) or major complications (e.g. wound infection, sepsis, pneumonia, peritonitis, abdominal abscess, and wound dehiscence) and not specified for postoperative intra-abdominal septic complications, by far the most feared complication.

In another study by Colombel *et al* of 270 CD patients, 26% received a stoma and 74% received stricturoplasty or one or more anastomoses⁸⁷. In that study, there was an obvious risk for selection bias when later analyzing all of the patients together, since high-risk patients were more likely to receive a stoma. No adverse effect was seen in the group receiving immunomodulators, but most of the patients were treated with steroids and only eight patients (3%) received immunomodulators alone and 33 patients (12%) received no medication prior to surgery. Furthermore, some of the patients received their immunomodulating therapy for less than two weeks prior to surgery, a time period that probably is too short to cause any negative effect¹¹⁶. At the same time patients who terminated their immunomodulation as late as four weeks prior to surgery were coded as not being on immunomodulation, a questionably short wash out period. Another issue with

this report is that anastomotic dehiscences (5%) were included in a larger group of septic complications together with e.g. wound infection, pneumonia, sepsis, bacteremia, and anastomotic complications and not analyzed alone.

The results of a study by Tay *et al* were in favour of improved perioperative outcome for patients with preoperative immunomodulation in 100 studied patients with CD going through primary surgery with anastomosis or strictureplasty¹¹⁴. Immunomodulators were analyzed together with biologics and further data regarding medications as well as the patients are limited in the report making it hard to evaluate. A more recent report from Japan found no influence of thiopurines on the surgical outcome, but numbers are small¹¹⁷.

In a report from the Mayo Clinic on ileal pouch anal-anastomoses in UC, rather than CD, an increased risk of infectious complications (anastomotic leak, pelvic abscess, or wound infection) were seen in patients pre-operatively treated with thiopurines in a univariate analysis (odds ratio=2.1; 95% CI, 1.1-4.3), but not after a multiple variable logistic regression analysis (odds ratio=1.3; 95 % CI, 0.6-2.9)¹¹⁵. Mahadevan *et al* studied the early outcome of ileal pouch-anal anastomosis in 209 patients with UC⁸⁸. Sixteen percent (9/55) of the patients on thiopurines had their immunomodulating therapy withdrawn as late as one week before surgery and were coded as not on immunomodulation. Among the remaining 46 patients with thiopurines, the rate of anastomotic complication was 9% compared with 6% in those without thiopurines (not significantly different). In their study, high-dose steroids and severe or fulminant disease according to Truelove-Witt criteria correlated with an increased risk of anastomotic complications ($p<0.01$). These studies on UC patients may also speak in favor of poor surgical timing rather than medication as only patients with on-going colitis would be in need of immunomodulators and in these cases a staged procedure is proposed¹¹⁸.

One major concern with all these studies is the substantial risk of selection bias as they are not really comparing patients with or without immunomodulation but rather two separate cohorts of patients; one with milder disease and one with more severe disease. Patients with more advanced Crohn's disease are obviously more likely to receive aggressive therapy, but also more prone to suffer surgical complications. One factor supporting this line of thinking is the increasing number of patients receiving immunomodulators over time^{70 95 96}.

A plausible explanation for this would be that the most severe patients are treated at an earlier stage with “new” drugs, may it be thiopurines, anti-TNF or vedolizumab and as care providers become more “at ease” with these therapies they spread to a broader population of CD patients. In our report thiopurine therapy in patients going through primary surgery was 4% compared to 19% among those operated before ($p < 0.001$) and treatment prior to surgery increased from 9% during the first seven years of the study period to 19% during the subsequent seven-year period ($p = 0.01$)⁷⁴.

Animal models

Animal models are far from surgery in severely ill, real-life patients, yet there are things we can learn from them. In the case of corticosteroids they have an adverse effect on the healing of bowel anastomoses, both in regards of obvious leaks as well as decreased bursting pressures¹¹⁹⁻¹²². A possible reason for this effect is inhibition of collagen synthesis through blocking of transforming growth factor β (TGF- β) and/or intercellular adhesion molecule-1 (ICAM-1)^{119 120 123 124}.

Azathioprine was tested in bronchial anastomoses and skin wounds on dogs by Lima *et al* who found that the breaking strength was at least halved in dogs treated with a combination of prednisolone (2 mg/kg) and azathioprine (1.5 mg/kg) compared to controls¹²⁵. In a study from our own group C57BL6 mice were randomly divided into two groups, with or without dextran sulfate sodium (DSS) induced colitis¹²⁶. The two groups were then further randomly divided into four groups each, receiving placebo, prednisolone (2 mg/kg bodyweight), azathioprine (5 mg/kg bodyweight) or infliximab (5 mg/kg bodyweight) during 14 days before surgery with a colo-colonic anastomosis. Bursting pressures were assessed two days later as a measure of anastomotic healing, and was found to be decreased in the prednisolone groups compared to all of the other three groups. There were no other significant differences between the groups, including azathioprine compared to placebo. Stolzenburg *et al*, who tested the anastomotic healing in rats using breaking strength, used up to four times as high dose of azathioprine as in the previous study but without any adverse effect on the breaking strength¹²⁷.

The use of tacrolimus has only been tested in two studies; in both cases confirming a detrimental effect on dermal healing^{128 129}. However, one of the studies also examined the bursting pressure in colonic anastomoses and found no influence of tacrolimus in comparison with controls¹²⁸.

Cyclosporine A has only been evaluated through breaking strength of dermal incisions in rats and was found to impair the breaking strength and accumulation of collagen in the wound compared to controls^{130 131}.

Mycophenolate mofetil has been studied in colonic anastomoses on rats with up to 40% reduction of the bursting pressure¹³². No effect was however seen on the synthesis of collagen in contrast to the effect of steroids. Instead, a decrease in acidic mucins was seen in mycophenolate mofetil treated animals, postulating a possible diminished protection of the healing process from luminal pathogens¹³². An interesting finding on the association between anastomotic healing and acidic mucins is the report by Egger *et al*¹³³. They administered keratinocyte growth factor to rats and found that bursting pressures were raised by 19-49% during the first seven days postoperatively ($p < 0.05$). At the same time an increase of the colonic crypt depth and acidic mucin content at the anastomosis ($p < 0.05$) was found but no difference in collagen deposition, promoting a possible role by the mucus in protecting the healing of a colonic anastomosis. Moreover, keratinocyte growth factor has been found to ameliorate the inflammation in DSS induced colitis in mice as well as trinitrobenzensulfonic acid (TNBS) induced colitis in rats^{134 135}.

In animal models broad inhibition of matrix metalloproteinases have shown an ameliorating effect on TNBS induced colitis^{136 137}. Further, such inhibition has shown increased bursting pressure by 28-48 % in colonic anastomoses on rats^{138 139} opening up an interesting field in regards of anti-inflammatory therapy as well as attempts of decreasing the surgical risks in CD. In the previously mentioned study from our own unit no signs were seen favoring an improvement of the bursting pressure by any of the anti-inflammatory therapies given compared with placebo¹²⁶.

The value of measuring or tapering drugs prior to surgery

The knowledge of how long the sustainability of the thiopurine effect is after withdrawal is scarce. In some studies six weeks were used as a pragmatic drug-free period prior to surgery as it is the time period possible to use clinically similar to the tapering of steroids⁷⁴¹⁴⁰. Further, in evaluating the thiopurine therapy it should probably have been ongoing for at least three months as it acts slowly and a possible clinical effect can be evaluated approximately ≥ 17 weeks after induction of remission in active disease¹¹⁶.

The most important issue in this regard is probably less exact cut off values but rather to have a good pre-surgical evaluation trying to diminish all possible risk factors^{69 71 74 79}.

Patients that are well optimized preoperatively are more likely to have a primary anastomosis without too much risk-taking¹⁴¹ whereas for patients who need under less fortunate circumstances a temporary double barrel stoma, often closed after a few months of recovery is the safer alternative¹⁴².

Postoperative recurrence of Crohn's disease

In historical studies, approximately 75% of CD patients underwent abdominal surgery at least once during their lifetime^{143 144}. The introduction of immunomodulators appeared not to have decreased the need for surgery up until the new millenium⁴⁰. More recent data suggest that surgery may now be less frequent, possibly owing to medical treatment with immunomodulators and biologicals. In a population-based Danish study 29% of newly diagnosed CD patients had undergone abdominal surgery within 7 years¹⁴⁵. Surgery is however not curative for CD which may recur anywhere in the gastrointestinal tract but typically in, or just proximal to, previous anastomoses or strictureplasties^{146 147}.

Endoscopic recurrence is apparent in a majority of patients already within the first year after resectional surgery for CD¹⁴⁸. Patients receiving placebo treatment in recent trials had severe endoscopic recurrence in 35% after 6 months¹⁴⁹, 58% after 1 year¹⁵⁰, 78% after 1 year¹⁵¹, 50% after 18 months¹⁵² and 64% after 2 years¹⁵³. The severity of endoscopic recurrence is generally graded according Rutgeerts' score¹⁵⁴. Endoscopic recurrence is associated with later clinical recurrence^{146 154} but many patients with endoscopic recurrence

remain asymptomatic, and the same applies to patients with a radiological recurrence. Symptomatic or clinical recurrence occurs in 20–40% within the first year after surgery in the placebo arms of most clinical trials¹⁴⁸. Hanauer *et al* reported clinical recurrence in as many as 77% within 2 years¹⁵³; whereas two other trials found clinical recurrence in 23%¹⁵⁵ and 45%¹⁵⁶ after 3 years. An observational population-based cohort study of patients diagnosed with CD before 1989 reported clinical recurrence after surgery in 44% after 10 years¹⁴³.

Surgical recurrence, i.e. recurrent disease requiring repeat surgery, occurred in 20–44% within 10 years after intestinal resection in older cohort studies^{157 158}. More recently Vester-Andersen *et al* found that 29% of patients in Copenhagen operated for Crohn's disease had a second resection within 5 years¹⁴⁵, other cohort studies including patients with prophylaxis found surgical recurrence in up to 50%^{147 159-162}.

The number one risk factor for postoperative recurrence of CD is smoking^{161 163-165}. A meta-analysis found a twofold increased risk of clinical recurrence and a 2.5-fold increase in surgical recurrence in smokers¹⁶⁶. Other patient-related factors such as age and gender has not convincingly been associated with the risk of recurrence^{167 168}. Penetrating disease^{163 169}, shorter duration of Crohn's disease before surgery^{161 167} and repeat surgery¹⁶⁸ all appear to be associated with an increased risk of recurrence. Disease location on the other hand does not obviously affect the recurrence rate, although coexistent peri-anal disease is associated with worse postoperative outcome^{167 168}. Histopathological factors such as presence of granulomas¹⁷⁰ and myenteric plexitis have also been associated with a higher risk of postoperative recurrence^{171 172}. Strictureplasties may be associated with higher risk of recurrence than resection^{173 174}.

With the exception of smoking habits, most of the established risk factors for postoperative recurrence cannot easily be influenced and several of them are in reality surrogate markers of aggressive or advanced disease.

Against this background, a key question is how to best avoid or defer recurrence and what place medical prophylaxis should have. Should all patients receive prophylactic drugs after resection for CD, or only patients at higher risk of recurrence? Is prophylaxis better started

immediately or when there is evidence of e.g. endoscopic recurrence? Which drug should be used?

Effectiveness of immunomodulators as prophylaxis against postoperative recurrence

A number of observational, mostly retrospective cohort studies have indicated that thiopurine analogues protect against postoperative recurrence^{147 159-162 175}. This review will however focus on the currently available randomized controlled trials of the subject.

6-mercaptopurin was compared to 5-ASA and placebo in a multicentre RCT including 131 patients with ileocolonic resection and anastomosis¹⁵³. 6-MP had a moderate and statistically significant effect on the risk of clinical recurrence within 24 months, which affected 50% (95% CI 34–68%) with 6-MP compared to 77% (61–91%) in the placebo group (HR 0.52). The risk of endoscopic recurrence was also reduced in the 6-MP group to 43% compared to 64% in the placebo group (HR 0.48). 5-ASA did not reach statistically significant superiority to placebo in any aspect.

Ardizzone *et al* randomized RCT 142 patients to receive either 5-ASA or azathioprine for postoperative prophylaxis after resection or strictureplasty for stricturing CD¹⁷⁶. At 24 months after surgery there was a trend towards less clinical as well as surgical relapses with azathioprine, but no statistically significant difference was found.

Herfarth *et al* briefly reported their RCT comparing 5-ASA and azathioprine¹⁷⁷. The study was stopped prematurely when an interim analysis made it clear that the hypothesis of superiority of AZA versus 5-ASA could not be tested with the planned sample size. Only 37 patients received treatment for a full year and treatment failure defined as clinical or severe endoscopic recurrence did not differ between the groups (9/18 with azathioprine vs. 9/19 with 5-ASA).

In another RCT, 81 patients with ileal or ileocolonic resection and anastomosis received in addition to metronidazole either azathioprine or placebo¹⁵¹. The risk of severe endoscopic

recurrence within 12 months was statistically significantly lower among patients on azathioprine by both intention-to-treat (55 vs. 78%) and per protocol (44 vs. 69%) analyses.

Peyrin-Biroulet *et al* performed a meta-analysis in 2009 including the four available randomized trials at the time¹⁷⁸ and concluded that prophylaxis with azathioprine and 6-MP is associated with a modest reduction (8–15%) in clinical recurrence compared to control groups receiving placebo, 5-ASA or metronidazole within the first postoperative year.

Reinisch *et al* interestingly included 78 patients operated for CD 6–24 months earlier with at least moderate endoscopic recurrence but without clinical recurrence (CDAI <200)¹⁷⁹.

Patients were randomized to receive either azathioprine or 5-ASA treatment, and the primary endpoint was treatment failure defined by worsened CDAI score or study drug discontinuation at 12 months. Clinical recurrence was significantly lower with azathioprine but at the same time discontinuation due to adverse events was significantly higher, and the frequency of treatment failure therefore did not differ between azathioprine and 5-ASA.

Savarino *et al* randomized 51 patients post resection for ileal or ileocolonic CD to receive adalimumab, azathioprine or 5-ASA¹⁸⁰. Although each group was small, the risks of endoscopic and clinical recurrence at 24 months were dramatically lower for patients receiving adalimumab with. Outcomes did not differ significantly between patients treated with azathioprine and 5-ASA.

In another Italian RCT, 22 patients operated with ileocolonic resection and considered to be at high risk of recurrence due to having at least two risk factors were randomized to infliximab or azathioprine prophylactic treatment¹⁸¹. As the trial was small, with no sample size calculation and un-blinded it was presented as a pilot study and the results should be interpreted with precaution. The primary endpoints endoscopic or clinical recurrence at 12 months did not differ significantly between the groups.

The above mentioned seven RCTs were all included in a 2014 Cochrane systematic review concluding that purine analogues may be superior to placebo for maintenance of surgically induced remission of CD but that the quality of evidence for this was low¹⁸². The relative efficacy of purine analogues to 5-ASA was uncertain due to conflicting results. The two trials

comparing azathioprine to infliximab or adalimumab indicate that adalimumab may be superior to azathioprine but the overall evidence level was considered to be very low.

The most comprehensive trial so far included 240 patients post ileocolonic or small bowel resection who were randomized to either azathioprine or placebo¹⁵⁵. The primary endpoint of the TOPPIC study was clinical recurrence within 3 years, occurring in 13% of patients receiving azathioprine and in 23% of patients given placebo (adjusted HR 0.54 (95% CI 0.27–1.06)). Most interestingly the protective effect was very pronounced among smokers (HR 0.13 (0.04–0.46)), whereas no protective effect at all was seen among non-smokers.

A recent RCT compared azathioprine with adalimumab in 81 patients and found no difference in endoscopic, radiological, clinical or surgical recurrence within the first year¹⁸³.

Data from pediatric cohorts are very limited both in number of studies as well as size of the studies and not further discussed in this review¹⁸⁴⁻¹⁸⁶.

In summary, there seems to be a modest protective effect from thiopurines against postoperative recurrence in CD. Most interestingly, the hitherto largest RCT (TOPPIC) suggested that this effect is completely explained by a dramatically reduced risk of recurrence among smokers, whereas non-smokers may not benefit from prophylaxis at all¹⁵⁵. No other drug including anti-TNF has convincingly proved superior to thiopurines for prophylaxis in CD.

Timing of prophylaxis

A retrospective study included 199 patients with ileocaecal resection for CD given immediate postoperative prophylaxis, tailored prophylaxis when endoscopic recurrence was confirmed, or no prophylaxis¹⁸⁷. The prophylaxis could be either antibiotics, mesalamine, thiopurines or anti-TNF. The HR for clinical recurrence in multivariable analysis was similar between tailored and immediate prophylaxis, but also with no prophylaxis at all. The

retrospective design and the associated risk of bias, as well as the multitude of studied drugs make the results difficult to interpret.

An attempt at avoiding these biases was made in an RCT including patients with resection and anastomosis for ileocolonic CD at four centres¹⁴⁹. Patients were randomized to receive azathioprine immediately (systematic) or to undergo ileocolonoscopy after 6 and 12 months and start azathioprine in case of endoscopic recurrence (Rutgeerts score $\geq$ 2) (endoscopy-driven). Endoscopic, radiological and clinical recurrence rates after 24 months were compared and no differences were found between systematic and endoscopy-driven prophylaxis. The study was stopped prematurely due to slow recruitment when only 63 patients had been included, compared to the intended sample size of nearly 250 patients. Again, this precludes any firm recommendations to be made.

The POCER trial was cleverly designed to study the optimal postoperative prophylaxis program and included 174 CD patients post resection with an endoscopically accessible anastomosis at 17 centers in Australia and New Zealand¹⁶⁵. Patients at low risk of recurrence were given no prophylaxis to begin with, those at high risk were given azathioprine and those at high risk who did not tolerate azathioprine were given adalimumab. All patients were then randomized to either an active arm including a colonoscopy at 6 months with treatment step-up if an endoscopic recurrence was found, or to a control arm with no surveillance colonoscopy. The primary endpoint was endoscopic recurrence at an 18-month colonoscopy which was significantly lower with the active care. There was also a non-significant trend towards better clinical outcome in the active arm.

The most recent retrospective cohort study compared the risk of surgical recurrence with systematic, endoscopy-driven and symptomatic-driven postoperative prophylaxis using azathioprine¹⁸⁸. The authors found that the risk of surgical recurrence was lower with either systematic or endoscopy-driven prophylaxis compared to azathioprine started upon clinical recurrence. However, this result will be biased by the fact that an unknown number of patients never had a clinical recurrence and thus the outcome for the larger group of patients who were given no prophylaxis until they had symptoms may be similar to those with systematic or endoscopy-driven prophylaxis. Nevertheless, the study does support

endoscopy-driven over systematic prophylaxis as it will avoid azathioprine for some patients and delay treatment start in others with the same risk of surgical recurrence.

In summary, the available results cannot really answer whether upfront prophylaxis or treatment started when endoscopic recurrence is evident is superior to prevent clinical or surgical recurrence. Direct evidence for selective prophylaxis to high risk patients is also lacking. The POCER trial showed that active endoscopic monitoring leads to better outcome¹⁶⁵.

Adverse events and cost

Thiopurines are known to cause a number of adverse events and previous cohort studies have indicated discontinuation rates between 9 and 39%¹⁸⁹. Discontinuation due to adverse events were also reported in the available RCTs and importantly most of these studies were blinded. The results were conflicting with higher discontinuation rate among patients receiving thiopurines than placebo or other control drugs in some^{176 177 179 183} but not in other studies^{151 153 180 181}. In the recent, large and double-blinded RCT comparing 6-mercaptopurine with placebo adverse events were at least as common among patients receiving placebo¹⁵⁵.

Studies of cost effectiveness of postoperative medical prophylaxis per se have shown conflicting results which is perhaps not very surprising given the uncertainty about the effectiveness of various drugs and regimens^{190 191}.

Conclusion

Many of the reports on the possible adverse effects by thiopurines and other immunomodulators lack in quality and differ too much in outcomes in order to perform a high quality meta-analysis. Moreover, many of the patients are often receiving more than one type of medication which tarnishes the picture even further. To verify if

immunomodulators and other modern anti-inflammatory therapies are interfering with the healing capacities or not require large randomized multi-center studies. One explanation to the different findings on the effect of these therapies may be that patients at one center are operated at a later stage of the disease compared with another center¹⁹². Thus these treatments may only act as surrogate markers for patients with a more severe illness, with an inherent healing disturbance or at least more prone to be associated with an increased risk of post-operative complications. Data speaking in this direction are the reports from Scarpa *et al* and Welsch *et al* where patients with CD suffering from postoperative complications had an increased risk of early surgical recurrences^{193 194}, warranting prophylactic thiopurine use according to the authors¹⁹³. This increased risk of early relapsing of the disease after a surgical complication may be the other way around; the early relapse is a signal of an aggressive disease which is associated with an increased risk of post-operative complications.

In the post-operative phase the available evidence suggests that thiopurines provide modest protection against postoperative recurrence in CD, with fewer recurrences than patients treated with placebo or 5-ASA. It remains uncertain whether prophylaxis with anti-TNF is more effective. Evidence for who should receive postoperative prophylaxis is also limited. Due to the mediocre effect, frequent adverse events and cost, most authors seem to agree that prophylaxis should not be started indiscriminately in all patients. The current ECCO guidelines recommend prophylaxis with thiopurines or anti-TNF to patients with at least one risk factor for recurrence¹⁶⁸. Smoking is a major risk factor for recurrence and the TOPPIC trial found a dramatically reduced risk of recurrence from azathioprine in smokers¹⁵⁵. Therefore, smokers who cannot be convinced to stop certainly should be considered for prophylaxis. Another option is to monitor patients with repeat investigations and initiate prophylaxis when endoscopic or radiological recurrence develops. The rationale to start medication in asymptomatic patients is that the disease otherwise will progress and that treatment at that point will be less effective. The problem with an endoscopy-driven approach however, is the very high occurrence of early endoscopic recurrence and critics argue that it may not be very predictive of clinical recurrence after all¹⁹⁵.

Some authors have suggested a regimen with immediate postoperative prophylaxis with thiopurines to high risk patients combined with endoscopic surveillance for all and step-up treatment if the disease relapses¹⁶⁷. Such an algorithm was studied in the POCER trial and the addition of endoscopic monitoring was found to reduce later endoscopic recurrence but again evidence of less clinical recurrence is lacking¹⁶⁵.

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