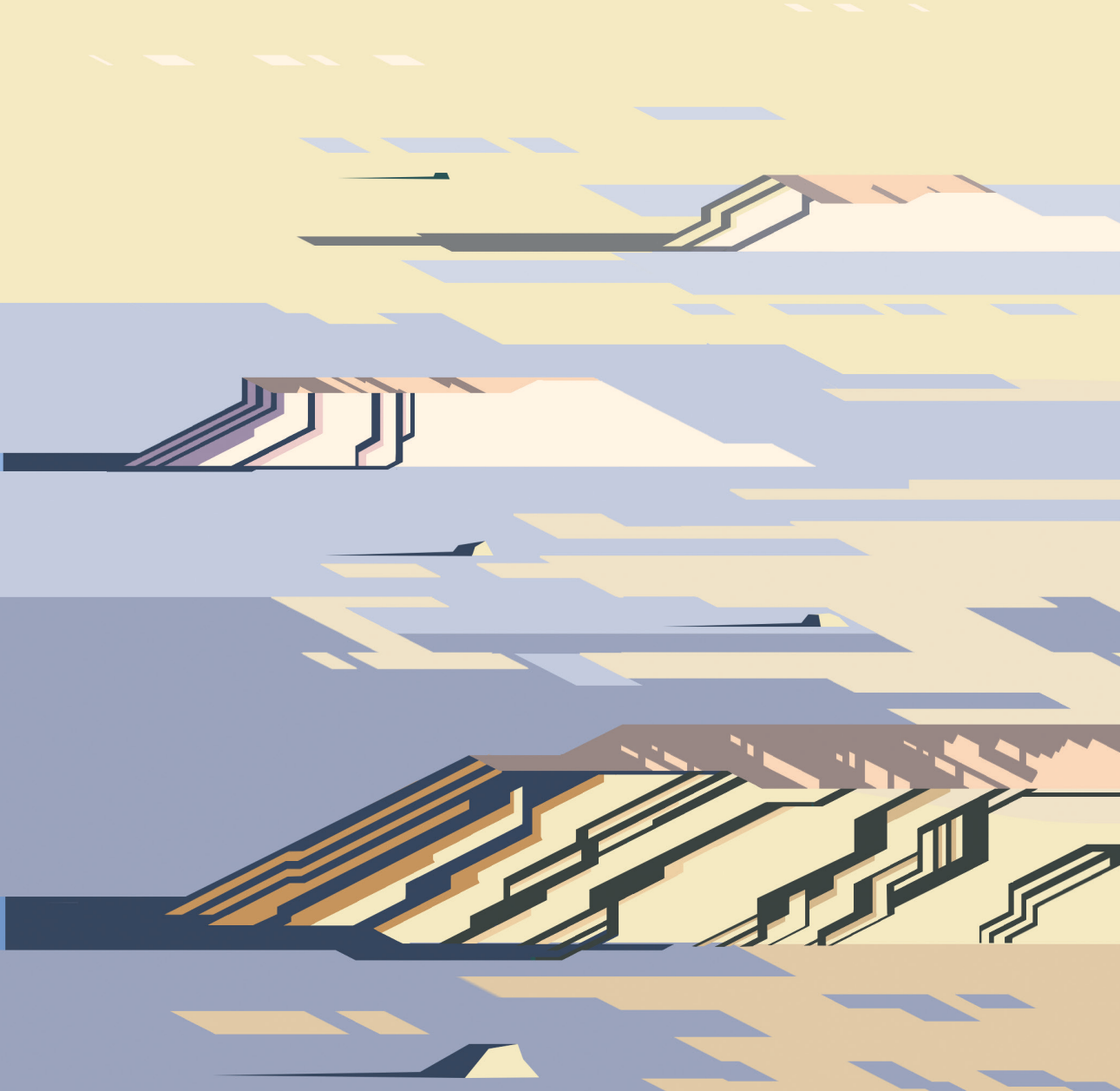
MANAGAMENT OF INFLAMMATORY BOWEL DISEASE
A LONG-TERM PERSPECTIVE



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MANAGAMENT OF INFLAMMATORY BOWEL DISEASE: A LONG-TERM PERSPECTIVE

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Management of inflammatory bowel disease: a long-term perspective

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Provided by thesis specialist Ridderprint, ridderprint.nl
Printing: Ridderprint
Layout and design: Garcella Dings, persoonlijkproefschrift.nl

ISBN: 978-94-6483-247-1

Publication of this thesis was financially supported by ChipSoft, Dr. Falk Pharma Benelux B.V., Ferring B.V., Nederlandse Vereniging voor Gastroenterologie, Stichting Fonds Ebe Brander and Teva Nederland B.V.

Management of inflammatory bowel disease: a long-term perspective

Behandeling van inflammatoire darmziekten:

een langetermijnsperspectief

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 28 september 2023 des middags te 4.15 uur

door

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geboren op 14 juli 1992
te Arnhem

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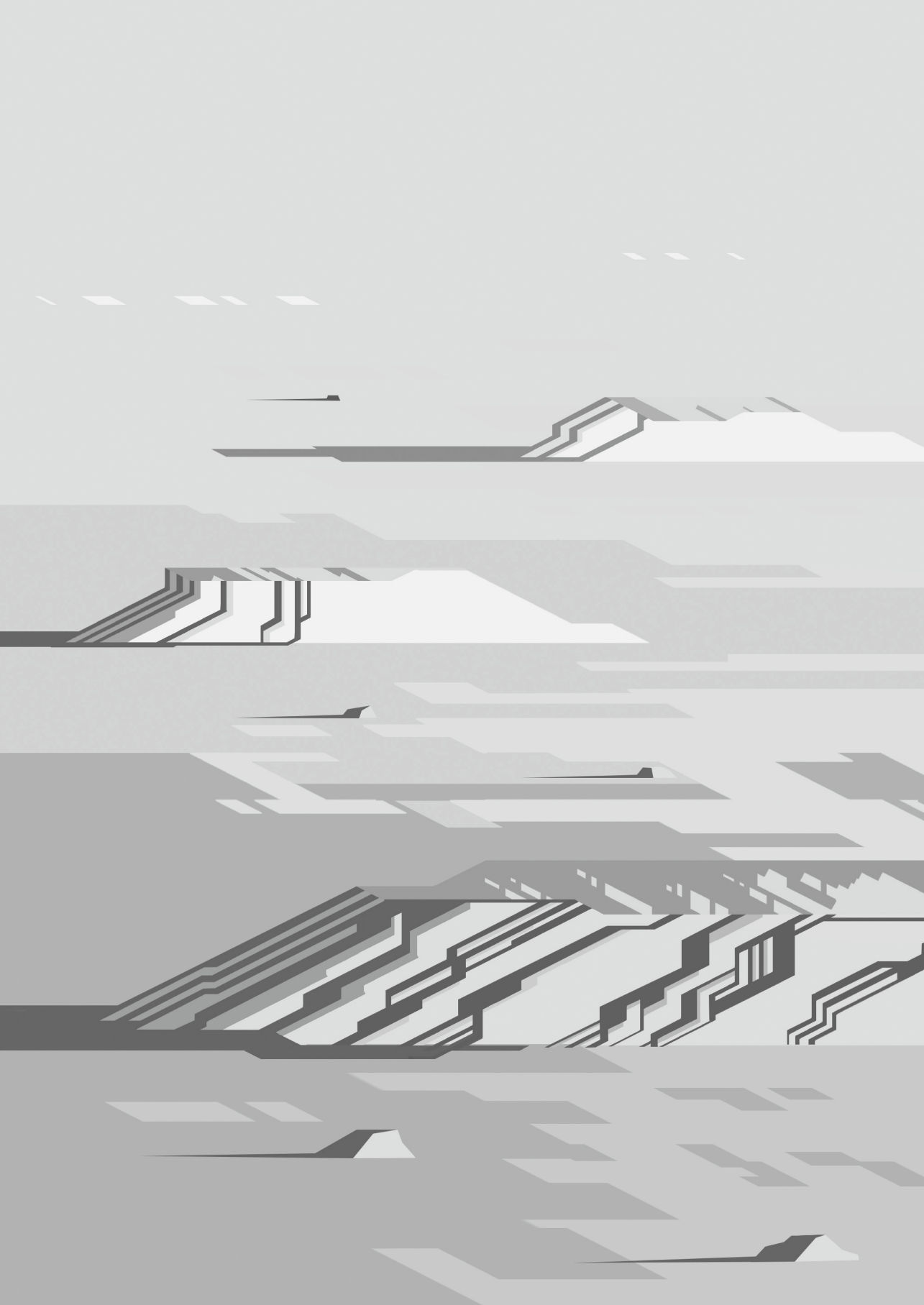
Dit proefschrift werd (mede) mogelijk gemaakt met financiële steun van ChipSoft, Dr. Falk Pharma Benelux B.V., Ferring B.V., de Nederlandse Vereniging voor Gastroenterologie, Stichting Fonds Ebe Brander en Teva Nederland B.V.

Table of Contents



CHAPTER 1

GENERAL INTRODUCTION

Overview

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing-remitting diseases of the gastrointestinal tract. During episodes of active inflammation, patients develop various symptoms, such as abdominal pain, diarrhea, rectal bleeding, weight loss and fatigue. In addition, accumulated bowel damage from inflammation can result in complications including intestinal strictures, intra-abdominal or perianal fistulae and abscesses in patients with CD[1,2] and colonic fibrosis and dysmotility in patients with UC.[1,3] In patients with longstanding, extensive IBD affecting the colon, the risk of colorectal cancer (CRC) is increased.[4]

In the short term, the therapeutic goal in patients with IBD is to relieve symptoms, primarily by dampening inflammation with immunosuppressive medication. In the long term, the goals of managing IBD are to prevent disease recurrences and IBD-related complications, thereby restoring quality of life and avoiding disability.[2,5] Meanwhile, the accompanying risks, burden and costs of medical therapy and endoscopic or surgical procedures should be acceptable.[2,5,6] Thus, the treatment must be tailored to the needs of the individual patient, which requires considerable knowledge, skill and expertise of the treating physician.

This thesis aims to address some of the challenges of long-term management of IBD. Section one includes four original studies on continuation versus withdrawal of long-term maintenance treatment with anti-tumor necrosis factor-α (anti-TNF) agents and concomitant immunomodulators (thiopurines or methotrexate). Section two reviews the practice of surveillance and management of colorectal dysplasia and cancer in patients with IBD, and includes two original studies investigating potential risk factors for colorectal dysplasia and cancer.

Background Section I

Biological treatment for IBD

The current paradigm for medical treatment of IBD is induction of remission, followed by maintenance therapy to prevent recurrence. In most patients, a step-up approach is used in which drugs with increasing potency are given sequentially, in case of insufficient response to the previous agent. Treatment response or remission should be confirmed objectively using biomarkers or endoscopy, in addition to improvement or resolution of symptoms.[6,7] The step-up approach usually starts with mesalamine (in UC patients) with or without rectal therapy, followed by immunomodulators, and finally advanced therapies including biologicals and *Janus kinase* (JAK) inhibitors.[8] In addition, corticosteroids are often used for remission induction, but are tapered as soon as possible to prevent side effects.[6] A top-down, rather than a step-up approach, may be preferred in patients presenting with severe inflammation or complications such as perianal fistulas. In these patients, biologicals can be started as a first-line treatment.[7,8]

Surgery is usually reserved for medically refractory disease, although results of early surgical intervention were comparable to biological treatment in a randomized trial in patients with ileal CD.[9]

Biologicals are a relatively novel class of drugs for the treatment of IBD. These compounds are intravenously or subcutaneously administered monoclonal antibodies targeting specific immunologic pathways that promote inflammation in IBD. The first biologicals registered for the treatment of IBD were infliximab and adalimumab, approved by the Food and Drug Administration (FDA) of the United States of America in 1998 and 2007, respectively.[10] Infliximab and adalimumab neutralize *tumor necrosis factor alpha (TNF-α)*, a pro-inflammatory cytokine produced mainly by macrophages, and are therefore referred to as *anti-TNF agents*.[11] Of note, the anti-TNF agents golimumab and certolizumab-pegol have also been approved by the FDA for UC and CD[10], respectively, but not by the European Medicines Agency (EMA). Therefore, these agents are rarely used in clinical practice in The Netherlands and are not discussed in this thesis.

Following the introduction of anti-TNF agents, biologicals with other mechanisms of action have received market authorization by the regulatory bodies (FDA and EMA) for treatment of IBD, including vedolizumab in 2014 and ustekinumab in 2016.[12,13] More recently, a new class of small molecules have been approved for UC, including tofacitinib (2018) and filgotinib (2021).[14,15] Both tofacitinib and filgotinib are JAK inhibitors, targeting an intracellular signaling pathway that promotes inflammation. The landscape of treatment options for IBD will continue to evolve in the near future, with several promising drugs currently under investigation.[16]

Even with biologicals and novel small molecules, the treatment of IBD remains challenging. With all available compounds, a substantial proportion of patients experiences *primary non-response*, i.e. induction therapy does not lead to improvement of symptoms or objective markers of inflammation. Furthermore, patients with a primary response remain at risk of a subsequent *loss of response*. Due to the risks of primary non-response and loss of response, after one year of starting treatment with either infliximab, adalimumab, ustekinumab, vedolizumab or tofacitinib, less than 50% of patients with CD or UC will achieve clinical remission.[12,13,17–23] Few data are available to guide the decision which of these compounds is most likely to induce and maintain remission in an individual patient, and only two head-to-head randomized controlled trials between any of these compounds have been conducted so far.[24,25]

Anti-TNF maintenance treatment

Infliximab and adalimumab have been shown to be effective for induction and maintenance of remission in CD and UC in randomized controlled trials with up to one year of follow-up.[18–21,26] In the real-world setting, it is estimated that 75-89% of patients treated with adalimumab or infliximab will have a sufficient primary response, and

subsequently continue maintenance treatment.[27–29] During maintenance treatment, the risk of loss of response to anti-TNF has been reported to be as high as 13-21% per year, mostly based on studies with 1-2 years of follow-up.[30–33] In contrast, some patients have a sustained benefit from anti-TNF treatment for more than 5 years.[27,34] The risk to benefit ratio of long term maintenance treatment with anti-TNF is unknown.

Loss of response to anti-TNF may occur due to formation of *anti-drug antibodies*. These antibodies can block the interaction between anti-TNF agents and the cytokine TNF-α, promote rapid clearance of anti-TNF agents, and eventually result in loss of response to anti-TNF agents. With repeated, drug-tolerant, scheduled measurements, anti-drug antibodies are detected within one year in 63% and 29% of patients treated with infliximab or adalimumab respectively, but a more than two-fold reduction of immunogenicity can be achieved by co-administration of an immunomodulator.[28] Indeed, combination therapy of infliximab with azathioprine is superior to infliximab or azathioprine monotherapy in both UC and CD.[35,36] In contrast, addition of azathioprine to adalimumab in patients with CD did not result in a higher proportion of patients achieving clinical remission.[37] Currently, international clinical guidelines uniformly advice to combine infliximab with an immunomodulator, while recommendations for adalimumab are diverging.[7,8,38–40]

The safety profile of anti-TNF agents is generally considered to be good, but side effects do occur. Although absolute risks are small, anti-TNF treatment is associated with hospitalization due to infections[41], and malignancies, including melanoma[42] and lymphoma[43]. Notably, the risks of severe infections and malignant lymphoma are highest among patients receiving a concomitant thiopurine.[41,43] Allergic reactions and infusion reactions are frequent, but can usually be managed without discontinuing the treatment.[44] Non-malignant skin manifestations such as psoriatiform dermatitis and eczema also occur frequently (20%), especially among young and/or female patients.[44]

Anti-TNF treatment is associated with high health care costs. In the Netherlands, costs of anti-TNF therapy accounted for 64% and 31% of the total health care expenditures in 2011 for CD and UC, respectively.[45,46] In recent years, the patents of infliximab and adalimumab have expired and *biosimilars* have entered the market. Biosimilars are monoclonal antibodies with an identical amino acid sequence, without clinically relevant differences in post-translational modification.[47] The use of biosimilars for adalimumab and infliximab is widespread in the Netherlands. As a result, the costs of anti-TNF treatment have probably fallen substantially, although no empirical evaluation of this cost reduction is available yet.[48]

Withdrawal of anti-TNF treatment

Elective withdrawal of anti-TNF treatment can be considered as a de-escalation strategy in IBD patients in stable remission, in order to reduce the risk of future drug-related adverse events (e.g. infections and malignancies), to meet patient preference and/or to provide cost savings.[49,50] The relapse rate after discontinuation of anti-TNF agents

in patients with IBD in remission is high, approximately 40% and 36% in patients with CD or UC within 1-2 years, respectively.[51] Based on randomized controlled trials, discontinuing infliximab in patients with IBD will lead 25-50% more relapses within one year, compared with infliximab continuation.[52–54] Fortunately, remission can be regained in 80% of patients with IBD by reintroducing the anti-TNF agent.[51]

A comprehensive risk assessment should be performed prior to withdrawal of anti-TNF treatment. Continuation of treatment may be more appropriate in patients with a more severe disease phenotype, such as patients with perianal disease, prior failure to biologicals, prior need for surgery or young age at IBD diagnosis.[55] Predicting the risk of relapse after withdrawal of anti-TNF treatment at the individual patient level is presently not possible. Established predictors of a lower risk of relapse, include low anti-TNF trough levels and confirmed endoscopic remission prior to treatment withdrawal.[56–58] The degree of endoscopic remission that should be obtained prior to withdrawal of anti-TNF remains unknown.

Theoretically, discontinuation of anti-TNF treatment may result in a significant reduction of pharmaceutical costs, but this should be balanced against a higher risk of relapse, potential loss in quality of life, and potential increases of other health care expenditures (e.g. hospitalization, surgery, escape treatment with more expensive novel therapies). Indeed, results from a health economic modelling study simulating infliximab (IFX) withdrawal in patients with CD in remission, suggests the following balance: discontinuation of anti-TNF slightly decreases quality of life, but saves € 73,133 per quality-adjusted life year (QALY) lost. The result of this model depends heavily on the pricing of IFX.[59] Whether € 73,133 per QALY is considered cost-effective also depends on the willingness to pay-threshold (approximately €80,000 per QALY in the Netherlands).[60] However, this threshold is usually applied to evaluate the cost-effectiveness of starting a therapy that increases quality of life, instead of stopping a therapy to save costs at the expense of a *decrease* in quality of life. While these results provide insight in the price-to-benefit ratio of continuation versus withdrawal of anti-TNF in CD, the cost-effectiveness of anti-TNF discontinuation in patients with UC remains unknown – especially when accounting for the introduction of biosimilars.

Withdrawal of concomitant immunomodulators

Among patients receiving anti-TNF combination therapy with an immunomodulator at the start of treatment, subsequent withdrawal of the immunomodulator during maintenance treatment can also be considered as a de-escalation strategy.[49,50] The increased risks of severe infections and malignant lymphoma with anti-TNF combination therapy versus monotherapy provide a strong rationale for this strategy.[41,43]

Three small randomized controlled trials compared withdrawal versus continuation of immunomodulators in patients with IBD in remission with infliximab or adalimumab. During 1-2 years of follow-up, no significant differences were detected in the rates of clinical

relapse, anti-TNF discontinuation and/or dose escalations.[61–63] However, all studies were underpowered to detect non-inferiority of the immunomodulator withdrawal strategy. Furthermore, one study reported an increase in C-reactive protein (CRP) and decrease in infliximab trough levels in the immunomodulator withdrawal group at the end of follow-up, suggesting that the incidence of loss of response to infliximab might be higher with longer follow-up.[61]

Three retrospective studies reported an association between the duration of combination therapy prior to withdrawal (with heterogeneous cut-offs of 6, 9 and 26 months, respectively) and the risk of relapse after immunomodulator withdrawal,[64–66] but two other studies found no association.[67,68] Additional predictors of relapse after immunomodulator withdrawal may include low infliximab trough levels or high CRP.[68] Further research is warranted to improve patient selection for immunomodulator withdrawal, and to determine the optimal duration of combination therapy.

Research questions addressed in section one of this thesis

Several knowledge gaps regarding long term maintenance treatment with anti-TNF agents are addressed in this thesis.

In **Chapter 2**, we aimed to compare the cost-effectiveness of continuation versus withdrawal of anti-TNF treatment in patients with UC in remission. To this end, a Markov state-transition model was constructed based on available evidence from prior literature, as well as input from an expert panel of Dutch gastroenterologists subspecialized in IBD.

In **Chapter 3,** the results of a multicenter prospective cohort study of patients with IBD in remission who discontinued anti-TNF treatment are reported. The objectives of this study were to 1) determine the risk of relapse after withdrawal of anti-TNF in a selected cohort of patients in confirmed endoscopic remission; 2) to assess whether the degree of endoscopic remission was related to the risk of relapse; 3) to identify predictors of relapse and 4) to establish whether remission could be re-established after reintroduction of anti-TNF.

Chapter 4 and **Chapter 5** describe the results of a retrospective study of patients receiving anti-TNF maintenance treatment in a general hospital and a tertiary referral center in The Netherlands between 2011 and 2019. In **Chapter 4,** the aim was to compare the risk of loss of response and anti-drug antibodies following withdrawal versus continuation of immunomodulators in IBD patients receiving combination therapy with infliximab or adalimumab. A secondary aim was to evaluate potential predictors of loss of response and anti-drug antibodies, including the duration of combination therapy prior to withdrawal.

In **Chapter 5**, the primary objective was to determine whether the incidence of loss of response to anti-TNF treatment declines with longer treatment duration. Secondary aims

were to identify predictors of loss of response with versus without anti-drug antibodies, and to assess the time-dependent risk of anti-TNF dose escalations and anti-TNF discontinuation.

Background Section II

Colorectal dysplasia and cancer surveillance in patients with IBD

The risk of colorectal cancer (CRC) is increased in patients with IBD, especially in case of a long disease duration and (a history of) extensive colitis, and in patients with a concomitant diagnosis of primary sclerosing cholangitis (PSC).[4,69–72] Colitis-associated CRC develops through several stages of precursor lesions, from healthy mucosa to low grade dysplasia (LGD), high grade dysplasia (HGD) and ultimately CRC.[73,74] All major gastroenterological societies recommend to perform surveillance colonoscopies in patients with left-sided or extensive UC or in patients with CD with at least 30% involvement of the colonic mucosa after 8-10 years of disease duration. IBD-colitis patients with concomitant PSC are considered eligible for surveillance, regardless of colonic disease extent and duration.[8,75–78]

Surveillance aims to reduce the risk of CRC with detection and removal of dysplastic precursor lesions. With novel endoscopic resection techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), even large -laterally spreading- lesions or lesions with advanced neoplasia (HGD or stage T1 CRC) can be removed endoscopically, instead of requiring total proctocolectomy.[79] Implementation of surveillance, along with improved endoscopic techniques for mucosal visualization and resection of lesions, as well as better control of inflammation with novel medical agents, may have contributed to the observed decrease in the incidence of colitis-associated CRC over time.[72,80,81] Nevertheless, the current practice of surveillance in patients with IBD is resource intensive and based on limited, retrospective, evidence, while interval carcinomas still occur.[82,83]

Risk factors for colorectal cancer and dysplasia

According to European as well as the latest North-American guidelines, the recommended surveillance interval is one, three or five years, depending on the presence of risk factors.[8,75,84] In European guidelines, these risk factors include a family history of CRC (first degree relative), a concomitant diagnosis of PSC, extensive colitis, the presence and severity of inflammation at endoscopic evaluation, a history of colonic dysplasia or a colonic stricture in the past five years, and presence of post-inflammatory polyps.[8,75] Ideally, the surveillance interval should not be determined based on the presence of individual risk factors, but on a validated prediction model that estimates the risk of colorectal cancer and dysplasia, based on multiple risk factors and their effect sizes.[85]

In this thesis, two potential risk factors for colorectal dysplasia and cancer are highlighted: presence of post-inflammatory polyps and the diagnosis of '*indefinite for dysplasia*'. In

patients with IBD with post-inflammatory polyps, European guidelines recommend to shorten the surveillance interval from five years to three years, in absence of other risk factors.[8,75] Post-inflammatory polyps, also referred to as pseudopolyps, are present in 20-45% of patients with colonic IBD.[86–89] Post-inflammatory polyps are polyp-like protrusions that are thought to develop as a result of regeneration and scarring of colonic mucosa after ulceration in IBD.[90] Although post-inflammatory polyps are not considered to be precancerous, their presence may reflect the severity of past inflammation, which is an established risk factor for colonic dysplasia and cancer.[85,89,90] Moreover, the presence of numerous post-inflammatory polyps can obscure otherwise visible dysplastic lesions, and limit the effectiveness of surveillance.[90] Post-inflammatory polyps have been linked to a higher risk of CRC in patients with IBD in older case-control studies,[87,88,91] but not in a more recent retrospective cohort study.[89] Therefore, it remains unclear whether post-inflammatory polyps are truly predictive of colorectal dysplasia and cancer in IBD, in absence of other risk-factors.

LGD can be difficult to distinguish from non-dysplastic mucosa, especially in the presence of active inflammation or epithelial regeneration following inflammation.[73] As there is considerable inter-observer variation in the diagnosis of LGD among pathologists, an independent confirmation by a second (expert) pathologist is recommended in most guidelines.[75,92–95] A diagnosis of *indefinite for dysplasia* (IND) can be made if no unequivocal distinction between LGD or non-dysplastic mucosa can be established.[73] Following a diagnosis IND, estimated risks of subsequent high grade dysplasia or cancer range widely between 1.0%-7.3% per patient-year, based on small studies with varying quality.[96–100] As the natural history of IND remains poorly understood, current guidelines offer no specific recommendations for the management of IND.[8,75–78]

Research questions addressed in section two of this thesis

The current practice of surveillance and management of colonic and cancer dysplasia in patients with IBD is reviewed in **Chapter 6** of this thesis. In addition to an up-to-date overview of this broad topic, we specifically discuss how recent technical advances in endoscopy impacted surveillance strategies, and detail options for endoscopic resection rather than surgical treatment of large dysplastic lesions. Finally, we outline several knowledge gaps that may guide future research.

In **Chapter 7**, the results from a retrospective cohort study in patients with IBD undergoing surveillance in a large referral center in the United States of America (Mount Sinai Hospital, New York) and seven hospitals in the Netherlands are presented. The primary objective was to determine whether post-inflammatory polyps predict the risk of colorectal dysplasia and cancer in patients with IBD. Secondary aims were to identify which patient and disease characteristics are associated with the presence of post-inflammatory polyps, and to describe the risk of colectomy in patients with IBD.

The risk of colorectal dysplasia and cancer following a diagnosis of IND is studied in **Chapter 8**, and compared with patients either without dysplasia or with LGD. This retrospective study is based on patients undergoing surveillance at the Mount Sinai Hospital, where all pathology specimens suspected for dysplasia were consistently reviewed by a panel of specialized pathologists, supervised by one expert pathologist during the entire study period.

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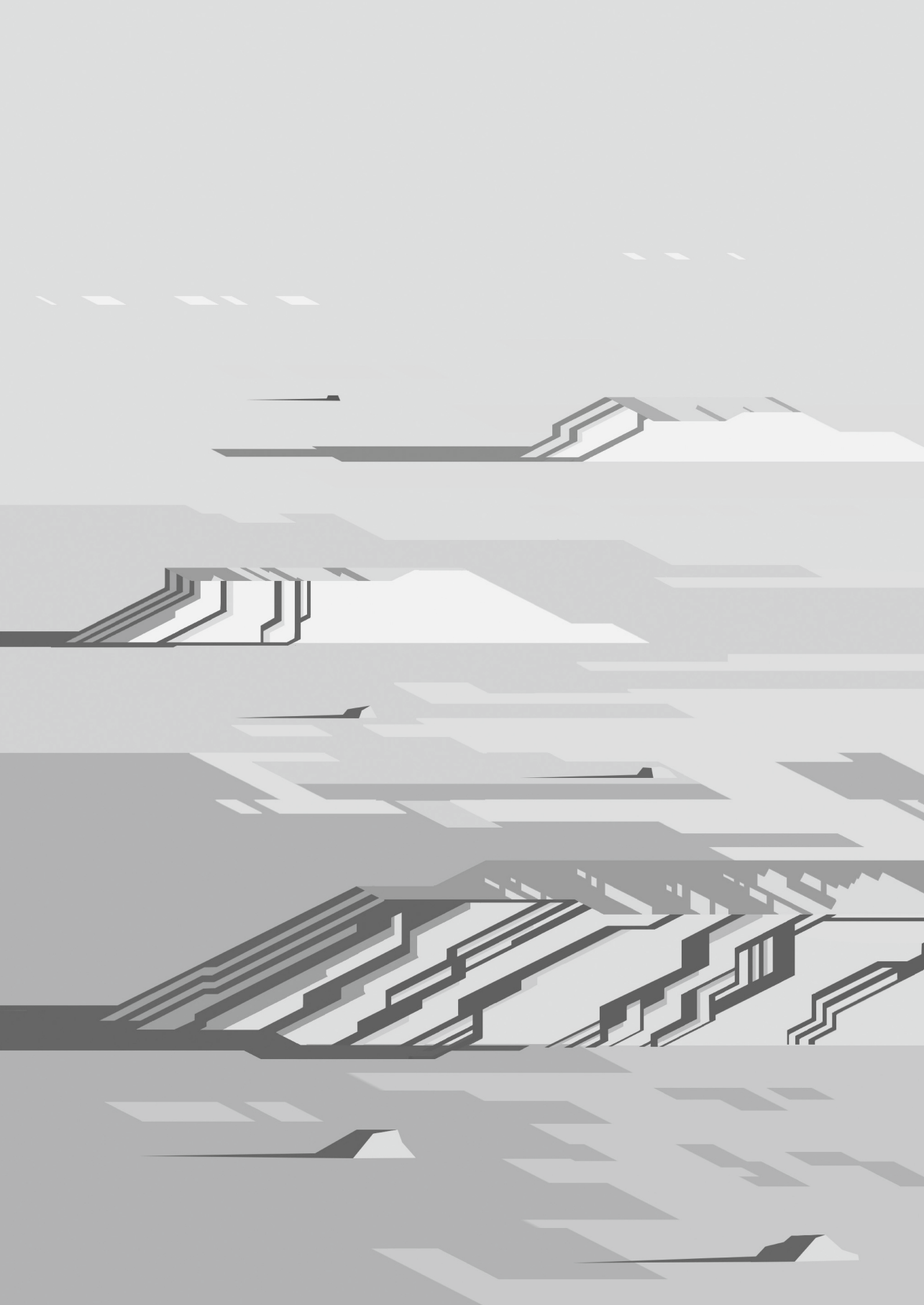
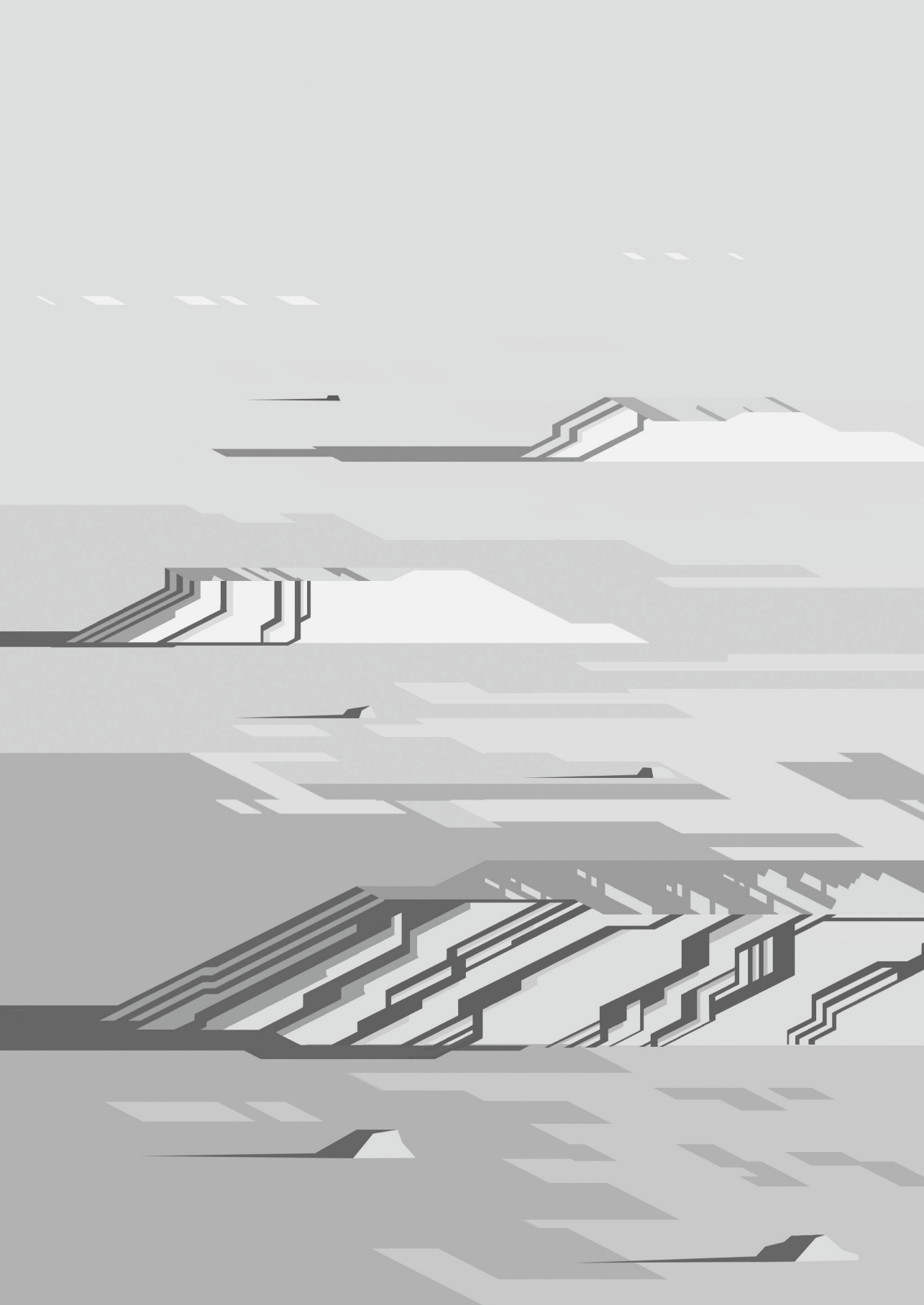


SECTION I

MAINTENANCE THERAPY WITH ANTI-TNF AGENTS AND THERAPEUTIC DE-ESCALATION



CHAPTER 2

Continuation of anti-TNF in patients with ulcerative colitis in remission is not cost-effective compared with treatment withdrawal: a Markov model

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Journal of Crohn's and Colitis 2021 May 4;15(5):709-718.

Abstract

Background and Aims

Anti-tumour necrosis factor alpha (anti-TNF) treatment accounts for 31% of health care expenditures associated with ulcerative colitis (UC). Withdrawal of anti-TNF in patients with ulcerative colitis (UC) in remission may decrease side effects and infections, while promoting cost containment. Approximately 36% of patients relapse within 12-24 months of anti-TNF withdrawal, but reintroduction of treatment is successful in 80% of patients. We aimed to evaluate the cost-effectiveness of continuation versus withdrawal of anti-TNF in patients with UC in remission.

Methods

We developed a Markov model comparing cost-effectiveness of anti-TNF continuation versus withdrawal from a health care provider perspective. Transition probabilities were calculated from literature, or estimated by an expert panel of 11 gastroenterologists. Deterministic and probabilistic sensitivity analyses were performed to account for assumptions and uncertainty. The cost-effectiveness threshold was set at an incremental cost-effectiveness ratio of €80,000 per quality-adjusted lifetime year (QALY).

Results

At 5 years, anti-TNF withdrawal was less costly (-€10,781 per patient), but also slightly less effective (-0.04 QALY per patient) than continued treatment. Continuation of anti-TNF compared to withdrawal costs €300,390/QALY, exceeding the cost-effectiveness threshold. Continued therapy would become cost-effective if the relapse rate following anti-TNF withdrawal was $\geq$43% higher, or if adalimumab or infliximab (biosimilar) prices fell below €87/40mg and €66/100mg, respectively.

Conclusions

Continuation of anti-TNF in UC patients in remission is not cost-effective compared to withdrawal. A stop-and-reintroduction strategy is cost-saving but is slightly less effective than continued therapy. This strategy could be improved by identifying patients at increased risk of relapse.

Keywords

Inflammatory bowel disease, treatment de-escalation, biosimilars

Introduction

Anti-tumour necrosis factor alpha (anti-TNF) agents have proven efficacy for induction and maintenance of remission in patients with Crohn's disease (CD) and ulcerative colitis (UC).[1,2] The safety profile of these compounds is generally considered to be good, but side effects including skin reactions,[3] and severe complications such as serious infections and melanoma or lymphoma do occur.[4–6] Moreover, treatment with anti-TNF is currently one of the main drivers of direct health care costs in inflammatory bowel disease (IBD), notwithstanding the recent introduction of biosimilars.[7,8] Although anti-TNF is less frequently prescribed in UC than in CD, 25% of the population of IBD patients treated with anti-TNF have UC, and the therapy accounts for 31% of health care expenditures in these patients.[7,9] Therefore, withdrawal of anti-TNF in patients with UC in remission could potentially eliminate side effects, infections and cancer risk, and reduce costs for society – provided that the relapse rate is acceptable.

Results from a Markov model simulating infliximab (IFX) withdrawal in patients with CD in remission, suggest that discontinuation of anti-TNF is not cost-effective, but cost-effectiveness depends highly on the price of IFX.[10] To date, however, no studies have been performed to evaluate the cost-effectiveness of withdrawal of anti-TNF treatment in patients with UC in remission. Therefore, the aim of this study was to assess the cost-effectiveness of anti-TNF continuation versus withdrawal in patients with UC in remission utilising a Markov model.

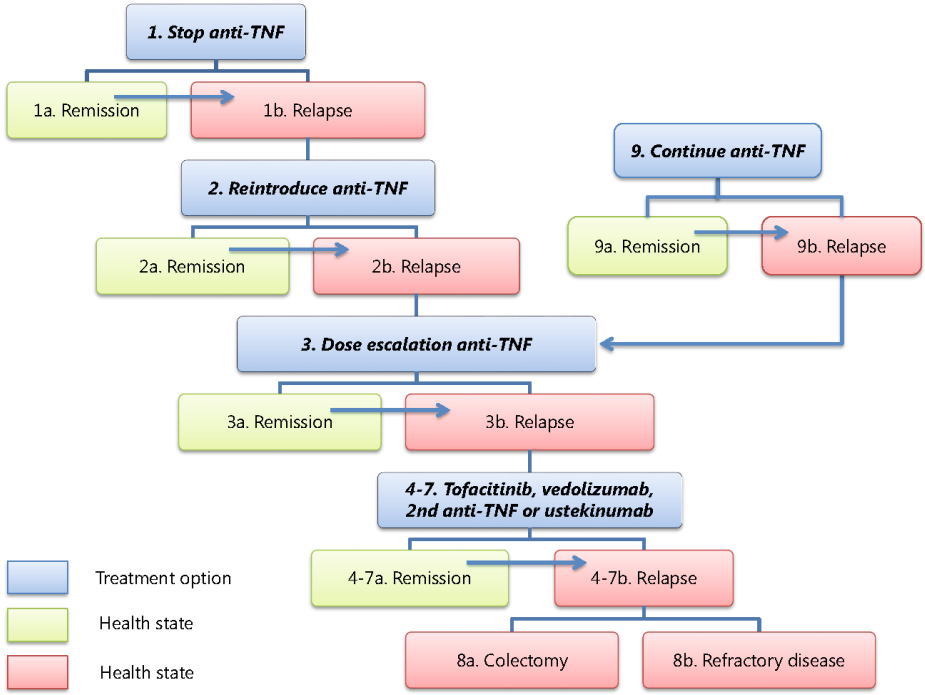
Methods

Model structure

A Markov state-transition model was constructed in order to predict the cost-effectiveness of continuation versus withdrawal of anti-TNF treatment from a health care provider perspective. The base case analysis represents a 40 year-old person with UC in remission for at least 1 year. The model structure is depicted in **Figure 1.** Within the model, patients could continue or stop anti-TNF treatment, reintroduce anti-TNF, escalate the dose of anti-TNF, switch to a second anti-TNF agent or another class of drugs (tofacitinib, vedolizumab or ustekinumab). After a non-response or loss of response to a second anti-TNF, tofacitinib, vedolizumab or ustekinumab, patients did not regain remission. Instead, these patients could undergo colectomy or enter a "refractory disease" state. The refractory disease state was characterised by persistent moderate-to-severe disease activity, despite medical treatment (tofacitinib, vedolizumab, dose escalated IFX or ustekinumab). For all 10 treatment options (except refractory disease and colectomy), patients could be in a state of either remission or relapse, thus creating a total of 18 health states. Each health state corresponded with a set of health care expenditures and utility weights enabling the calculation of costs and *quality-adjusted lifetime years* (QALYs). The model employed pre-set transition

probabilities to calculate transitions between health states in a 3-monthly cycle for a timespan of 5 years. The model was constructed in Microsoft Excel 2010 (available upon request from corresponding author).

Figure 1. Graphical representation of the Markov model



Transition Probabilities and Expert Panel

Three-monthly transition probabilities were calculated as weighted averages from previously published studies, preferably recent meta-analyses **(Table 1)**. In order to restrict the number of assumptions underlying the model, a survey was filled out by 11 gastroenterologists specialised in IBD from 10 different hospitals in the Netherlands (2 from tertiary referral centres, 9 from general hospitals). This expert panel estimated the likelihood of several treatment options in the model (**Table 1**), and frequencies of resource use per health state (**Supplementary Table 1**). Mean estimates were analysed for relative percentages, while median estimates were imported in the model for other parameters.

Table 1. Three-monthly transition probabilities

Parameter	Transitions[1]	Probability	Source
Based on previously published studies			
Relapse after withdrawal of anti-TNF	1a → 1b		
Year 1		0.064	27,28
Year 2		0.036	27,28
Year 3-5		0.027	28
Remission after reintroduction of anti-TNF	1b → 2a	0.67	27,28
Relapse after reintroduction of anti-TNF	1b → 2b	(1-0.67)	27,28
LOR to reintroduced anti-TNF [2]	2a → 2b	0.035	29
Remission after dose-escalation	2b → 3a	0.30	27,28
Relapse after dose-escalation	2b → 3b	(1-0.30)	27,28
Clinical response to tofacitinib	3b → 4a	0.58	20–22,43
Non-response to tofacitinib	3b → 4b	(1-0.58)	20–22,43
LOR to tofacitinib	4a → 4b	0.09	20–22
Clinical response to vedolizumab	3b → 5a	0.56	25
Non-response to vedolizumab	3b → 5b	(1-0.58)	25
LOR to vedolizumab	5a → 5b	0.014	44
Clinical response to 2nd anti-TNF	3b → 6a	0.41	45
Non-response to 2nd anti-TNF	3b → 6b	(1-0.41)	45
LOR to 2nd anti-TNF	6a → 6b	0.22	45
Clinical response to ustekinumab	3b → 7a	0.62	24
Non-response to ustekinumab	3b → 7b	(1-0.62)	24
LOR to ustekinumab	7a → 7b	0.11	24
LOR to anti-TNF	9a → 9b	0.0174	13
Clinical response to dose-escalation	9b → 3a	0.60	46–49
Non-response to dose-escalation	9b → 3b	(1-0.60)	46–49
LOR dose-escalated anti-TNF	3a → 3b	0.066	46,47
Based on Expert Panel [3]			
Agent of choice after relapse on dose escalated anti-TNF			
Tofacitinib	2b → 4a/4b	0.12 (0.1)	
Vedolizumab	2b → 5a/5b	0.40 (0.3)	
Second anti-TNF	2b → 6a/6b	0.28 (0.2)	
Ustekinumab	2b → 7a/7b	0.20 (0.1)	
Treatment for refractory disease			
Colectomy	4-7b → 8a	0.37 (0.3)	
Medical therapy	4-7b → 8b	0.63 (0.3)	

Table 1. Three-monthly transition probabilities (continued)

Parameter	Transitions[1]	Probability	Source
Agent of choice for refractory disease			
Tofacitinib	Within 8b	0.40 (0.2)	
IFX 10mg/kg per 8 weeks	Within 8b	0.07 (0.09)	
Ustekinumab	Within 8b	0.34 (0.2)	
Vedolizumab	Within 8b	0.19 (0.1)	

1) Reported transitions correspond to Figure 1. 2) no data available for UC. Based upon incidence of IFX failure in CD between 3-12 months after reintroduction of anti-TNF, excluding patients with primary non-response. LOR: loss of response. 3) Values reported as mean (SD).

Assumptions

The age-adjusted mortality rate was derived from StatLine, a database from the Dutch governmental organisation *Statistics Netherlands*.[11] The mortality rate was kept constant in all health states, except for increased mortality (1.1%) in the first 3-month cycle following colectomy.[12]

Various assumptions were made to establish the model. In the base case analysis, we assumed that 72% of patients were on IFX, and 28% on ADA.[13] Use of golimumab and certolizumab-pegol was ignored to simplify the model. We assumed that in all patients who relapsed after withdrawal of anti-TNF, the first choice would be to reintroduce this same compound and – if unsuccessful – escalate the dose, prior to a switch to another drug. In the model, colectomy indicates a subtotal colectomy with construction of an ileostomy.

Concomitant use of azathioprine and mesalamine was analysed to calculate costs, but did not impact transition probabilities due to lack of data. Use of concomitant mesalamine or thiopurines was deemed negligible for patients treated with tofacitinib, vedolizumab or ustekinumab. Finally, the expert panel's estimates excluded surveillance colonoscopies and routine blood tests for thiopurine use. We modelled 4 blood tests per year for patients on azathioprine, and at least 1 colonoscopy per 5 years for all patients to account for surveillance.

Costs and utility weights

Pharmaceutical costs and costs of health care procedures were derived from the Dutch National Health Care Institute, Dutch National Health Care Authority and prior publications.[14–17] All were based on, or indexed to, 2018 prices. Unit costs with corresponding references are presented in **Supplementary Table 2.** Importantly, there is heterogeneity in reported costs of IFX and ADA since the introduction of biosimilars for IFX and ADA in 2015 and 2018 respectively. For the base case analysis a price of €120/40mg ADA and €200/100mg IFX was assumed. Subsequently, the effect of a wide range of prices was analysed.

Frequencies of resource use per health state were based on standard doses and regimens for medication, and estimates by the expert panel for other costs (**Supplementary Table 1**). In addition, several one-off expenses were applied in the model. Diagnostic costs (colonoscopy, routine lab, outpatient visit, faecal calprotectin and anti-TNF trough level measurement) were applied to patients in whom anti-TNF was discontinued. Surgical costs and 12 days of hospitalisation (expert panel; interquartile range 8.5-15.5 days) were applied at the time of colectomy. Induction costs were applied when anti-TNF, vedolizumab, tofacitinib or ustekinumab were (re)started.

Utility weights for remission (0.87), mild disease (0.76), moderate-to-severe disease (0.41), and patients with an ileostomy (0.72), were based on a prior study.[18] All relapses were considered mild, while refractory disease was considered moderate-to-severe. Patients who underwent colectomy were considered to have severe disease during 3-months to account for perioperative morbidity, and then transitioned to the utility weight for patients with an ileostomy.[18]

Costs and QALYs were discounted at a rate of 4% and 1.5% per year respectively.[16] Throughout this manuscript, discounted costs and QALYs are reported, unless stated otherwise.

Primary outcome

The primary outcome was the *incremental cost-effectiveness ratio (ICER)* for continuation versus withdrawal of anti-TNF, defined as:

$$ICER = \frac{\Delta\, costs}{\Delta\, QALY} = \frac{Costs\ of\ continuation - Costs\ of\ withdrawal}{QALY\ of\ continuation - QALY\ of\ withdrawal}$$

Cost-effectiveness was defined as an ICER below €80,000/QALY, corresponding to the cost-effectiveness threshold in the Netherlands.[19]

Sensitivity analyses

One-way deterministic sensitivity analyses were performed. Input parameters (transition probabilities, utility weights and costs) were altered one by one with a range of +/-20% to assess the individual impact on the ICER. In addition, probabilistic sensitivity analyses were performed to account for uncertainty in transition probabilities and utility weights, which were assumed to follow a beta distribution. Beta distribution parameters were based on either the number of events versus non-events, or standard deviations reported in included studies. Input parameter ranges and beta distribution parameters are reported in **Supplementary Table 2 and Supplementary Table 3**. A Monte Carlo simulation was performed with 1000 iterations to calculate 95% confidence intervals for costs and QALYs. The proportion of simulations resulting in an ICER that is considered cost-effective was displayed in a cost-effectiveness acceptability curve.

Results

Base Case Analysis

Continuation of anti-TNF was not cost-effective compared to withdrawal of anti-TNF, with an ICER of €300,390/QALY (**Table 2).** Withdrawal was less costly and only slightly less effective. At 5 years, costs of withdrawal of anti-TNF were €21,768, yielding 4.06 QALYs per patient, versus €32,549 for 4.09 QALYs for continuation of anti-TNF. Discontinuation of anti-TNF resulted in a large decrease in pharmaceutical costs for IFX and ADA and a decrease in costs of intravenous administration of medication and measurement of trough levels, which offset the moderate increase in all other costs (**Figure 2**).

The model resulted in a cumulative incidence of relapse after withdrawal of anti-TNF of 23%, 44% and 52% at 1,2 and 5 years respectively, but the majority of patients were able to regain remission. Still, during the timespan of the model, cessation of anti-TNF resulted in a consistently smaller proportion of patients in remission over time, with a mean difference of

-3.9%, and a maximum difference of -6,5% at 0.75 years **(Figure 3).** At 5 years, the cumulative incidences of refractory disease (9.4% versus 7.7%) and colectomy (4.0% versus 3.2%) were higher in patients who had stopped anti-TNF versus those who had continued anti-TNF (**Figure 3)**, while cumulative mortality was 0.005% in both groups.

Table 2. Results of the base case analysis

	Withdrawal of Anti-TNF	**Continuation of anti-TNF**	**Incremental results** (withdrawal - continuation)
Discounted			
Life years	4.51	4.51	0
QALYs	4.057	4.093	- 0.04
Costs	€21,786	€32,549	- €10,781
ICER			**€300,390 / QALY**
Undiscounted			
Life years	4.99	4.99	0
QALYs	4.216	4.254	- 0.04
Costs	€24,499	€36,305	- €11,805
ICER			**€314,426 / QALY**

ICER**,** Incremental cost-effectiveness ratio; QALY, Quality adjusted lifetime year.

Figure 2. Breakdown of incremental costs for withdrawal of anti-TNF versus continuation of anti-TNF. Cost are represented as incremental costs/patient per 5 years.

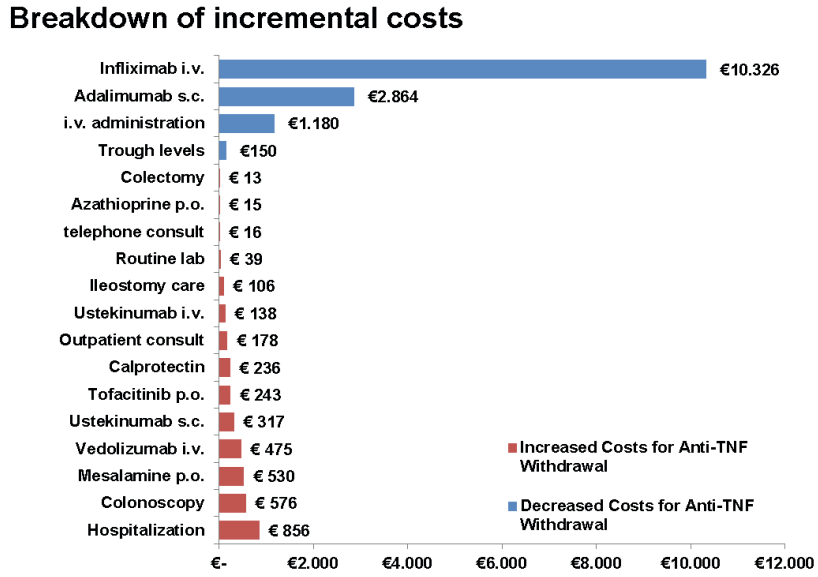
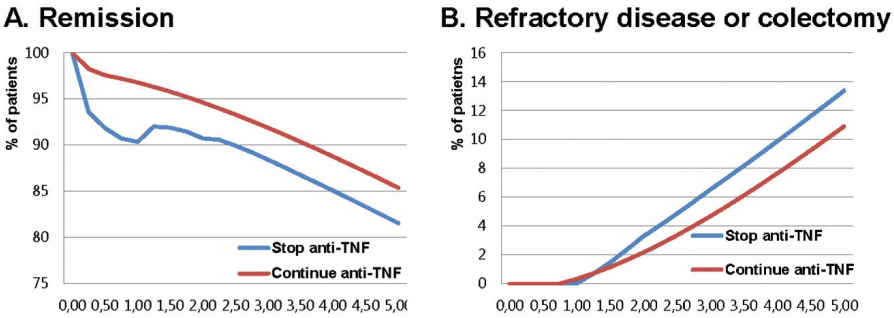


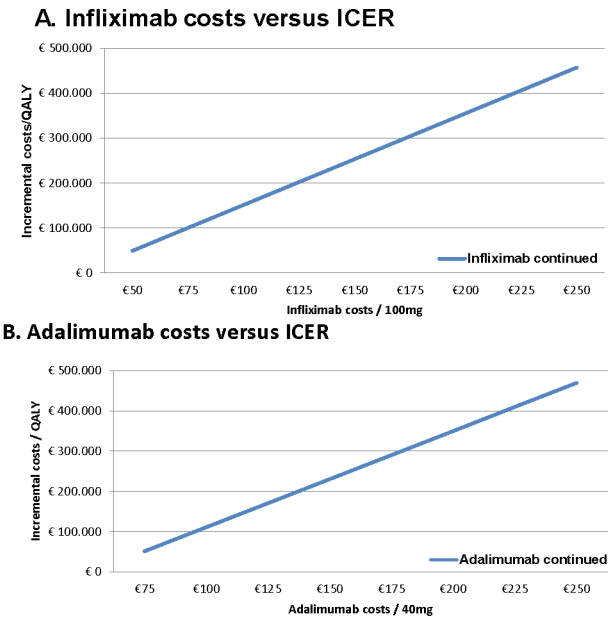
Figure 3. Clinical outcomes of the base case analysis over time. A) Proportion of modelled patients in remission. B) Cumulative incidence of refractory disease and colectomy.



Adalimumab versus infliximab

Subgroup analyses for anti-TNF agent revealed that neither continuation of ADA (ICER €159,133/QALY), nor continuation of IFX was cost-effective (ICER €355,324/QALY) compared to the stop-and-reintroduction strategy. However, cost-effectiveness depends on unit costs for ADA and IFX (**Figure 4)**. Continuation of IFX became cost-effective if IFX prices fell below €66/100mg, and continuation of ADA became cost-effective at prices below €87/40mg.

Figure 4. Impact of pharmaceutical costs on the ICER for withdrawal versus continuation of anti-TNF. A) IFX/100mg, B) ADA/40mg.



Deterministic sensitivity analyses

The main conclusion that continuation of anti-TNF is not cost-effective compared to withdrawal of anti-TNF could not be reversed by +/-20% variation in any of the individual input parameters. However, if the initial outcomes after withdrawal of anti-TNF were 20% worse than expected (i.e. a higher relapse rate, or lower probability of response to anti-TNF reintroduction), the predicted costs per QALY (€300,390) for continued therapy were halved (**Figure 5a**). Likewise, the ICER decreased with a lower incidence of loss of response to continued anti-TNF use, or increased probability of response to subsequent dose-escalation. Furthermore, quality of life weights for patients in remission or mild disease could impact the relative cost-effectiveness of anti-TNF continuation versus withdrawal (**Figure 5b**), while unit costs other than IFX and ADA had little impact on the primary outcome (**Figure 5c**).

Figure 5. One-way deterministic sensitivity analyses for A) transition probabilities, B) utility weights and C) costs.

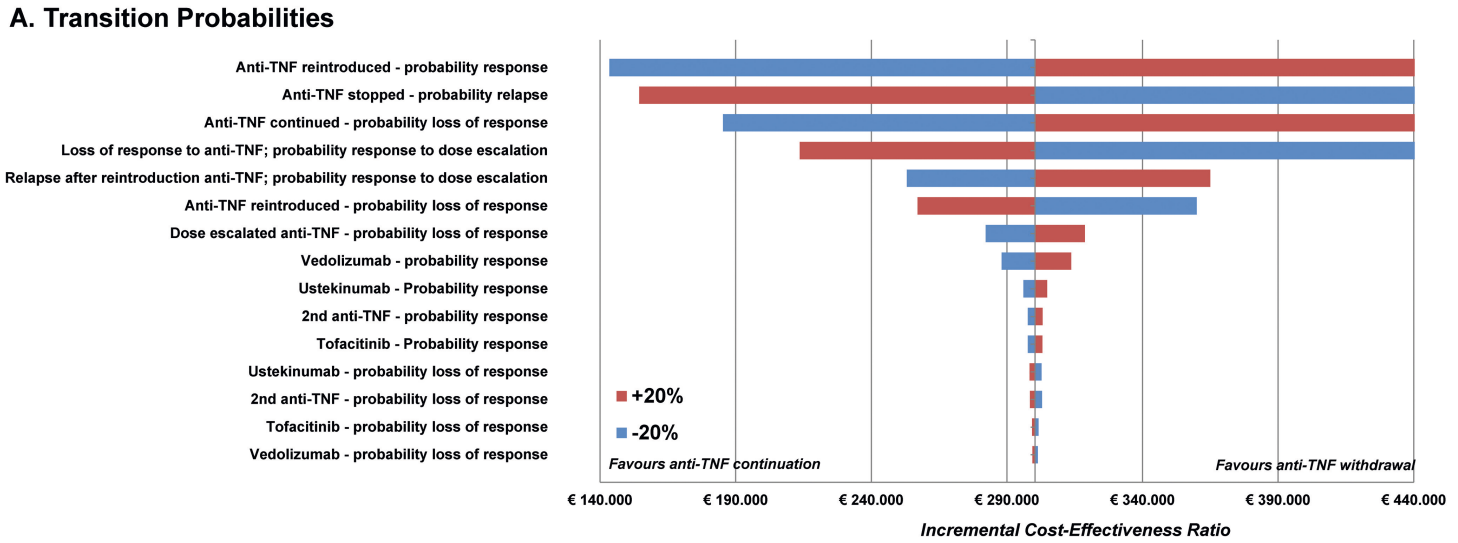
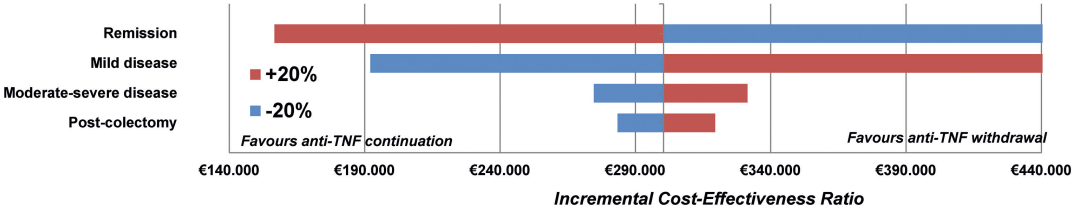
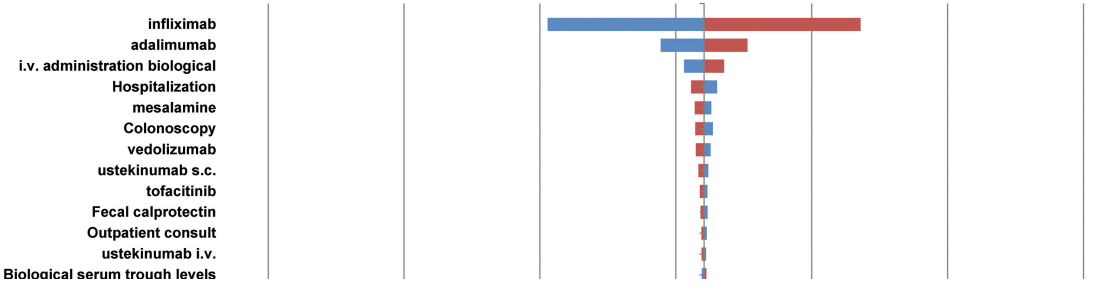


Figure 5. One-way deterministic sensitivity analyses for A) transition probabilities, B) utility weights and C) costs. (Continued)

B. Utility Weights



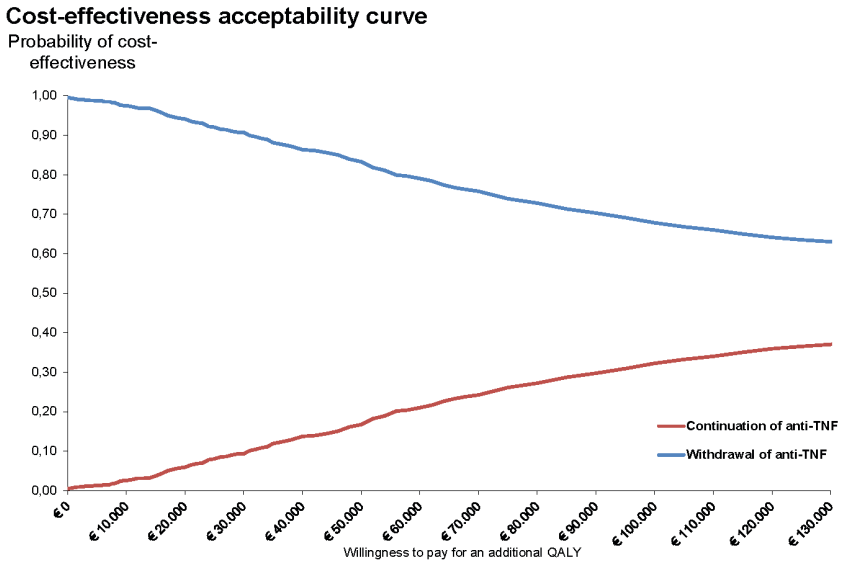
C. Costs



Probabilistic sensitivity analyses

Based on 1000 Monte Carlo simulations, withdrawal of anti-TNF resulted in a mean difference of -0.04 (95%CI: -0.21; 0.13) QALYs and -€10,405 (95%CI: -€22,991; -€1,618) in health care expenditures per patient per 5 years, compared to continuation of anti-TNF. At the cost-effectiveness threshold of €80,000/QALY, continuation of anti-TNF was not cost-effective compared to withdrawal in 72.8% of the simulations (**Figure 6)**. When utility weights were kept constant and only transition probabilities were altered, withdrawal of anti-TNF again resulted in decreased expenditures (-€10,707; 95%CI: -€23,044 ; -€1,655), and a loss in QALYs of -0.04 (95%CI -0.14 ; 0.11) and treatment continuation failed to achieve cost-effectiveness in the majority of simulations (73.1%). Illustrations of the probabilistic sensitivity analyses are presented in **Supplementary Figure 1.**

Figure 6. Cost-effectiveness acceptability curve for withdrawal versus continuation of anti-TNF based on probabilistic sensitivity analysis.



Scenarios

Scenario sensitivity analyses were performed to examine the impact of treatment choices, employing remission rates instead of response rates, incidence and severity of relapses, and the potential of a risk-stratified protocol for anti-TNF withdrawal.

Continuation of anti-TNF was not cost-effective compared to withdrawal of anti-TNF, regardless of the medical agent of preference after a relapse on dose-escalated anti-TNF (Figure 1, health state 3B). The resulting ICER was €302,949 if all patients switched to tofacitinib, €354,642 for vedolizumab, €251,053 for a second anti-TNF and €290,547 for ustekinumab.

A sensitivity analysis was performed in which all patients without complete clinical remission upon introduction of tofacitinib, ustekinumab, vedolizumab or a second anti-TNF were considered as relapses, and thus entered the refractory disease state or underwent colectomy. For this analysis, three-month clinical remission rates (tofacitinib: 0.21 [20–23]; ustekinumab: 0.16 [24]; vedolizumab: 0,32 [25], second anti-TNF: 0,12 [26]) were used instead of clinical response rates (**Table 1)**. With these stricter definitions for remission, continuation of anti-TNF was still not cost-effective (ICER: €248,350).

If the relapse rate after withdrawal of anti-TNF increased by ≥43% during the 5-year timespan, corresponding to a cumulative incidence of relapse of 32%, 45% and 66% at 1, 2 and 5 years respectively, continued anti-TNF therapy became cost-effective. Furthermore, if all relapses in the model were considered moderate-to-severe (0.41) instead of mild (0.76), continuation of anti-TNF was still not cost-effective, but a large decrease in the ICER (€130,683) occurred.

We examined the cost-effectiveness of anti-TNF withdrawal in all patients, to a hypothetical risk-stratified protocol that identifies patients at high risk for relapse. **Supplementary Figure 2** displays the minimal requirements for the protocol, to be more cost-effective compared to anti-TNF withdrawal in all patients, at a cost-effectiveness threshold of €80,000. As the number of patients considered at high risk for relapse increases, the necessary reduction of the relapse rate in patients who withdraw anti-TNF increases. For example, a protocol that identifies 10% or 20% of the patients as high risk, would have to result in a decreased relapse rate of 5% or 10% respectively, to be more cost-effective than withdrawal of anti-TNF in all patients.

Discussion

Despite the fact that the introduction of biosimilars has resulted in a sharp reduction of costs, continuation of anti-TNF in patients with UC in remission was not cost-effective compared to withdrawal of anti-TNF based on a Markov model. The stop-and-reintroduction strategy led to a modest reduction in costs at 5 years (-€10,781 per patient) compared to continued therapy, but the difference in quality of life (-0.04 QALY) was so small, that the ICER for continued therapy versus withdrawal (€300,390/QALY) exceeded the pre-specified cost-effectiveness threshold. Continuation of anti-TNF therapy would become cost-effective at prices below €66/100mg for IFX, and €87/40mg for ADA.

Several studies have shown that the relapse rate after withdrawal of anti-TNF in UC is considerable. A meta-analysis reported a cumulative incidence of relapse of 36% at 12-24 months, with estimates from individual studies ranging from 11-59%.[27] Short-term outcomes after reintroduction are excellent, with 80% of patients achieving remission[27], of whom 67% will achieve remission within 14 weeks.[28] Long-term remission after reintroduction of anti-TNF has not been studied in UC and was assumed to be similar to CD in our model.[29] These

findings are key to interpreting our results. In our model, more than 50% of patients relapsed and required reintroduction of anti-TNF before 5 years – but the high likelihood of regaining remission resulted in a limited loss of quality of life. Meanwhile, savings in pharmaceutical costs for IFX and ADA outweighed the increase in diagnostic costs and pharmaceutical costs of second-line treatments.

The current consensus according to the European Crohn and Colitis Organisation guidelines, as well as recently published reviews, is that withdrawal of biologicals in IBD requires a personal approach, with consideration of risk factors and patients' preferences.[30–32] Our results confirm that risk-stratification is potentially more cost-effective than withdrawal of anti-TNF in all patients. Few studies, however, have identified risk factors for relapse after withdrawal of anti-TNF in patients with UC, such as prior use of biologicals.[33] Notably, a large retrospective study including 324 patients with UC was unable to identify risk factors for relapse after withdrawal of anti-TNF (although disease extent was predictive in the subgroup of patients in deep remission).[28] This is in contrast to cohorts of patients with CD (or IBD cohorts with a majority of CD patients) where multiple predictors for relapse after withdrawal of anti-TNF have been identified, such as young age at diagnosis[34,35], strictures[28] and male sex[36], while low anti-TNF trough levels are protective.[36,37] Moreover, the relapse rate in prior literature is mostly based on retrospective studies, and likely reflects a selected population of patients judged to be at low risk of relapse by their treating physicians. In our model, a 43% increase in the relapse rate following cessation of anti-TNF would make continuation of therapy cost-effective compared to withdrawal. This is still within the range reported in prior studies.[27] Therefore, our results provide a rationale for withdrawal of anti-TNF, but should not replace the current practice of case-by-case evaluation.

An important strength of our analysis is that we not only explored the initial outcomes after withdrawal of anti-TNF, but also took the possibility of regaining remission upon treatment with a second anti-TNF or novel therapy into account. Furthermore, the cycle of 3 months in our analysis corresponds with the duration of induction regimens of IFX, vedolizumab and ustekinumab – and reflects the time needed to evaluate the treatment response in routine clinical practice. This may explain the large difference in the ICER for continuation versus withdrawal of anti-TNF between our study in UC and a study simulating IFX withdrawal in CD (€300,390 versus €73,133, respectively).[10] In that study, patients were considered refractory after failure on dose-escalated anti-TNF – which could occur within 4 months of anti-TNF withdrawal. Furthermore, the model employed a higher relapse rate following anti-TNF withdrawal, which is in accordance with the literature for CD.[27,36]

Inevitably, our model could not capture the full complexity of anti-TNF treatment for UC, leading to several limitations. Importantly, the model represents a health care provider perspective and includes direct health costs only. Productivity loss constitutes 31% of UC-related costs and has been shown to be increased in active disease and following colectomy.[38–40] It is conceivable that the reduction in direct costs associated with withdrawal

of anti-TNF is partially offset by an increase in productivity loss. Obviously, productivity loss can only be assessed reliably in empirical studies comparing withdrawal versus continuation of anti-TNF in UC. Incorporating indirect costs would have required numerous, country-specific assumptions that would not have improved the validity and generalisability of our model. Likewise, lack of specific data limited incorporating the incidence of adverse events and side effects, such as infections and skin-reactions[3,4], or potentially better outcomes in patients continuing an immunomodulator after anti-TNF withdrawal.[28] It should also be noted that the studies included in the model to calculate transitions between health states were not homogenous, including meta-analyses, retrospective cohort studies and randomised controlled trials. Consequently, various definitions were used for remission versus relapse, either based on clinical, biochemical or endoscopic findings – or on drug discontinuation in retrospective studies. In general, we chose to include the definition that was most likely to elicit therapeutic action (dose escalation or step-up of therapy), as the associated costs and QALY's would have the largest impact on the outcomes of our analysis. A sensitivity analysis with stricter definitions for remission did not alter our conclusion that continuation of anti-TNF is not cost-effective. Finally, our model represents a European health care setting and may not be directly generalisable to other health care systems. Mean annual costs in our model were €4354 and €6510 for withdrawal versus continuation of anti-TNF, corresponding roughly to a European cohort reporting annual costs of €2,088 for all UC patients, and €7,359 for 20% of patients with highest costs within 5 years of diagnosis.[41] However, for example, annual costs in the USA are estimated at $51,429 (€43,521) and $14,151 (€11,975) for UC patients on (non-biosimilar) anti-TNF or immunosuppressants, respectively.[42] Although higher pharmaceutical costs in the USA would most likely underscore our finding that continuation of anti-TNF is not cost-effective compared to withdrawal of anti-TNF, this cannot be concluded from our results.

In addition to providing a rationale for withdrawal of anti-TNF to promote cost containment, our results also provide insight into areas of particular importance for further research in patients with UC. This should include accurate determination of the relapse rate and identification of patients at high risk for relapse, while also establishing predictors for successful reintroduction of anti-TNF. Furthermore, as in CD[29], studies with long follow-up in UC patients are needed to assess the incidence of treatment failure and colectomy after anti-TNF withdrawal. Ideally, such studies should also assess quality of life, direct health care costs and productivity loss following withdrawal of anti-TNF.

In conclusion, we report that continuation of anti-TNF is not cost-effective in patients with UC in remission compared to withdrawal of anti-TNF. A withdrawal strategy with reintroduction of anti-TNF upon relapse, results in a decrease in health care expenditures with a limited loss in quality of life. Lower drug prices due to the introduction of biosimilars can make continuation of anti-TNF more attractive in patients with a more severe disease phenotype. Until a risk-stratified approach is validated prospectively, an individual approach with careful consideration of risks and benefits, as advocated by current guidelines, is highly appropriate.

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Supplementary Table 1. Yearly costs per health state and frequencies of resource use

Health State	Yearly costs €	Lab[1] Median (IQR)	FCP[1] Median (IQR)	Trough levels[1] Median (IQR)	Colonoscopy[1] Median (IQR)	IV Infusions % patients
Anti-TNF stopped						
Remission	1,230	2 (2.0-2.5)	3 (2.0-3.5)	NA	0.2 (0.0-0.3)	NA
Relapse	4,921	8 (4.0-8.0)	8 (8.0-8.0)	NA	3.2 (2.9-3.4)	NA
Anti-TNF reintroduced						
Remission	5,850	2 (2.0-2.0)	2 (2.0 – 2.8)	1 (1.0-1.0)	0 (0.0-0.2)	72
Relapse	10,346	8 (8.0-8.0)	8 (8.0 – 8.0)	4 (4.0-4.0)	1.3 (0.9-1.6)	72
Anti-TNF dose-escalated						
Remission	10,000	2 (2.0-2.5)	2 (2.0-2.3)	1 (1.0-1.5)	0 (0.0-0.2)	72
Relapse	18,415	8 (8.0-8.0)	8 (8.0-8.0)	4 (4.0-4.0)	3.6 (2.8-4.0)	72
Tofacitinib						
Remission	12,238	2.5 (2.0-3.0)	2 (2.0-2.5)	NA	0 (0.0-0.2)	NA
Relapse	21,861	8 (8.0-8.0)	8 (8.0-8.0)	NA	4 (3.7-4.0)	NA
Vedolizumab						
Remission	15,649	2.5 (2.0-3.0)	2 (2.0-2.5)	1 (0.1-1.0)	0 (0.0-0.2)	100
Relapse	30.104	8 (8.0-8.0)	8 (8.0-8.0)	4 (3.0-4.0)	4 (3.7-4.0)	100
Ustekinumab						
Remission	25,475	2.5 (2.0-3.0)	2 (2.0-2.5)	1 (0.1-1.0)	0 (0.0-0.2)	NA
Relapse	24,201	8 (8.0-8.0)	8 (8.0-8.0)	4 (3.0-4.0)	4 (3.7-4.0)	NA
2nd anti-TNF agent						
Remission	4,862	2.5 (2.0-3.0)	2 (2.0-2.5)	1 (1.0-1.0)	0 (0.0-0.2)	28
Relapse	14,776	8 (8.0-8.0)	8 (8.0-8.0)	4 (4.0-4.0)	4 (3.7-4.0)	28
Refractory Disease	27,727					
Infliximab		4 (3.3-4.0)	4 (3.0-4.0)	1 (1.0-1.8)	0.4 (0.3-0.6)	100
Vedolizumab		4 (3.3-4.0)	4 (3.0-4.0)	1 (0.8-1.5)	0.4 (0.3-0.6)	100
ustekinumab		4 (3.3-4.0)	4 (3.0-4.0)	1 (0.8-1.5)	0.4 (0.3-0.6)	NA
Tofacitinib		4 (3.3-4.0)	4 (3.0-4.0)	NA	0.4 (0.3-0.6)	NA
Anti-TNF continued						
Remission	5,662	2 (1.5–2.0)	2 (1.0-2.0)	1 (0.6-1.0)	0.2 (0.0-0.2)	72
Relapse	8,468	6 (5.0-8.0)	8 (8.0-8.0)	4 (4.0-5.0)	2 (2.0-2.4)	72

Supplementary Table 1. Yearly costs per health state and frequencies of resource use (continued)

Health State	Outpatient Visit[1] Median (IQR)	Telephone consult[1] Median (IQR)	Hospitalisation[1] Median days (IQR)	Azathioprine[1] % patients	5-ASA[1] % patients
Anti-TNF stopped					
Remission	2 (2.0-2.5)	1 (0.3-2.0)	NA	50 (30-68)	90 (70-95)
Relapse	8 (4.0-8.0)	4 (4.0-4.0)	2.8 (1.7-5.3)	50 (30-68)	90 (70-95)
Anti-TNF reintroduced					
Remission	2 (1.5-2.0)	1 (0.5-2.0)	NA	80 (78-90)	90 (70-93)
Relapse	8 (5.0.10.0)	4 (4.0-7.0)	5.6 (2.0-10.9)	80 (78-90)	90 (70-93)
Anti-TNF dose-escalated					
Remission	2 (1.5-2.0)	1 (0.5-2.0)	NA	80 (78-90)	90 (70-93)
Relapse	8 (6.0-8.0)	8 (4.0-8.0)	11.2 (6.3-17.1)	80 (78-90)	90 (70-93)
Tofacitinib					
Remission	2 (2.0-2.5)	1 (1.0-2.0)	NA	NA	NA
Relapse	8 (6.0-15.0)	4 (4.0-8.0)	14 (7.0-20.0)	NA	NA
Vedolizumab					
Remission	2 (2.0-2.5)	1 (1.0-2.0)	NA	NA	NA
Relapse	8 (6.0-15.0)	4 (4.0-8.0)	14 (7.0-20.0)	NA	NA
Ustekinumab					
Remission	2 (2.0-2.5)	1 (1.0-2.0)	NA	NA	NA
Relapse	8 (6.0-15.0)	4 (4.0-8.0)	14 (7.0-20.0)	NA	NA
2nd anti-TNF agent					
Remission	2 (2.0-2.5)	1 (1.0-2.0)	NA	80 (78-90)	90 (70-93)
Relapse	8 (6.0-15.0)	4 (4.0-8.0)	14 (7.0-20.0)	80 (78-90)	90 (70-93)
Refractory Disease					
Infliximab	3 (3.0-4.0)	2 (0.8-2.5)	28 (11.1-39.0)	80 (78-90)	90 (70-93)
Vedolizumab	3 (3.0-4.0)	2 (0.8-2.5)	28 (11.1-39.0)	NA	NA
ustekinumab	3 (3.0-4.0)	2 (0.8-2.5)	28 (11.1-39.0)	NA	NA
Tofacitinib	3 (3.0-4.0)	2 (0.8-2.5)	28 (11.1-39.0)	NA	NA
Anti-TNF continued					
Remission	2 (1.0-2.0)	1 (0.5-1.3)	NA	50 (38-55)	70 (55-85)
Relapse	6 (4.0-8.0)	4 (4.0-7.0)	2.0 (1.5-4.6)	50 (38-55)	70 (55-85)

NA, Not applicable 1) Based on Expert Panel. Note that patients can remain in one "Relapse" state for a maximum of 3 months (except MRD). Post-colectomy costs are not reported in this table, but were €6,979 based on an empirical study[14].

Supplementary Table 2. Unit costs and corresponding references

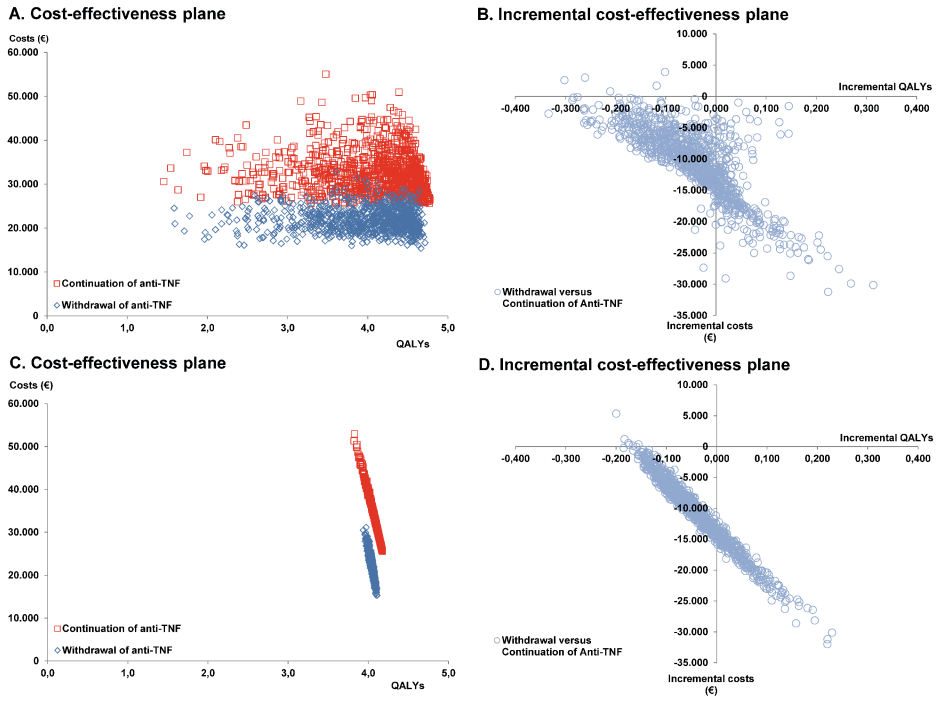
	Price (€)	Range deterministic Sensitivity analysis (€)	Source
Lab			
Routine blood tests	18.56	14.85 – 22.27	16,17
Faecal calprotectin	48.63	38.90 – 58.36	17
Biological serum trough levels	68.21	54.57 – 81.85	A
Hospital resource use			
Outpatient consult	94.70	75.76 – 113.64	16
Telephone consult	37.63	30.10 – 45.16	16
Hospitalisation (1 day)	495.35	396.28 – 594.42	16
Ileostomy care and supplies (yearly)	6979.14	5,583.31 – 8,374.97	14
Procedures			
Colonoscopy	428.82	343.06 – 514.58	17
Subtotal colectomy	8,198.16	6,558.53 – 9,837.79	A
i.v. administration biological (once)	87.88	70.30 – 105.46	A
Medication (yearly)			
Adalimumab[1]	3,120.00	2,496.00 – 3,744.00	B
Infliximab[2]	4,550.00	3,640.00 – 5,460.00	B
Vedolizumab[3]	14,552.52	11,642.02 – 17,463.02	15
Tofacitinib[4]	11,782.26	9,425.81 – 14,138.71	15
Ustekinumab[5]	13,849.67	11,079.74 – 16,619.60	15
Azathioprine[6]	92.22	73.78 – 110.66	15
Mesalamine[7]	744.81	595.85 – 893.77	15
One-off expenditures[10]			
Evaluation of disease activity prior to anti-TNF withdrawal[9]	658.92	NA	16,17, A
Colectomy + hospitalisation	14,142.32	NA	A
Adalimumab induction[8]	660.00	NA	B
Infliximab induction[8]	1,970.08	NA	15,B
Vedolizumab induction[8]	5,624.84	NA	15,A
Ustekinumab induction[8]	13,436.33	NA	15,A
Ustekinumab i.v.(90mg, once)	3,384.12	2,707.30 – 4,060.95	15
Tofacitinib induction[8]	2,039.24	NA	15

1) 40mg/2weeks; 2) 350mg/8 weeks; 3) 300mg/8 weeks; 4) 5mg BID; 5)90mg / 12 weeks; 6) 100mg/day; 7)2400mg/day 8) added costs during first three months, based on standard induction regimen (medication costs and intravenous administration costs) minus costs of 3 months maintenance therapy. 9) colonoscopy, outpatient visit, routine lab, faecal calprotectin, biological serum trough level. 10) Not included in deterministic sensitivity analysis as these are combinations of individual costs reported above. **A:** Personal communication. **B:** expert opinion.

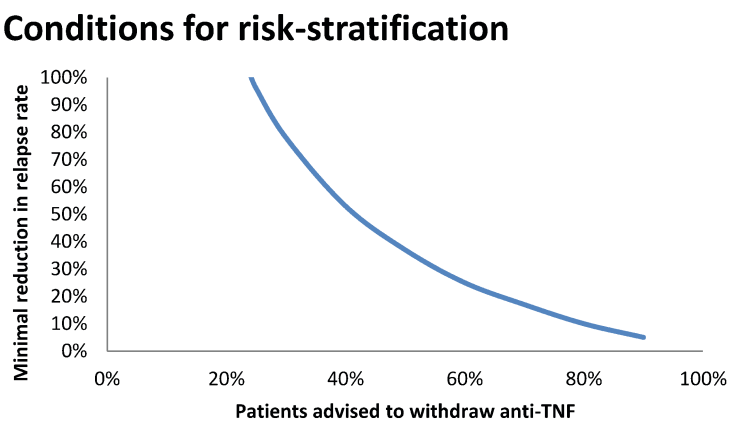
Supplementary Table 3. Transition and utility parameter ranges and distribution for sensitivity analyses

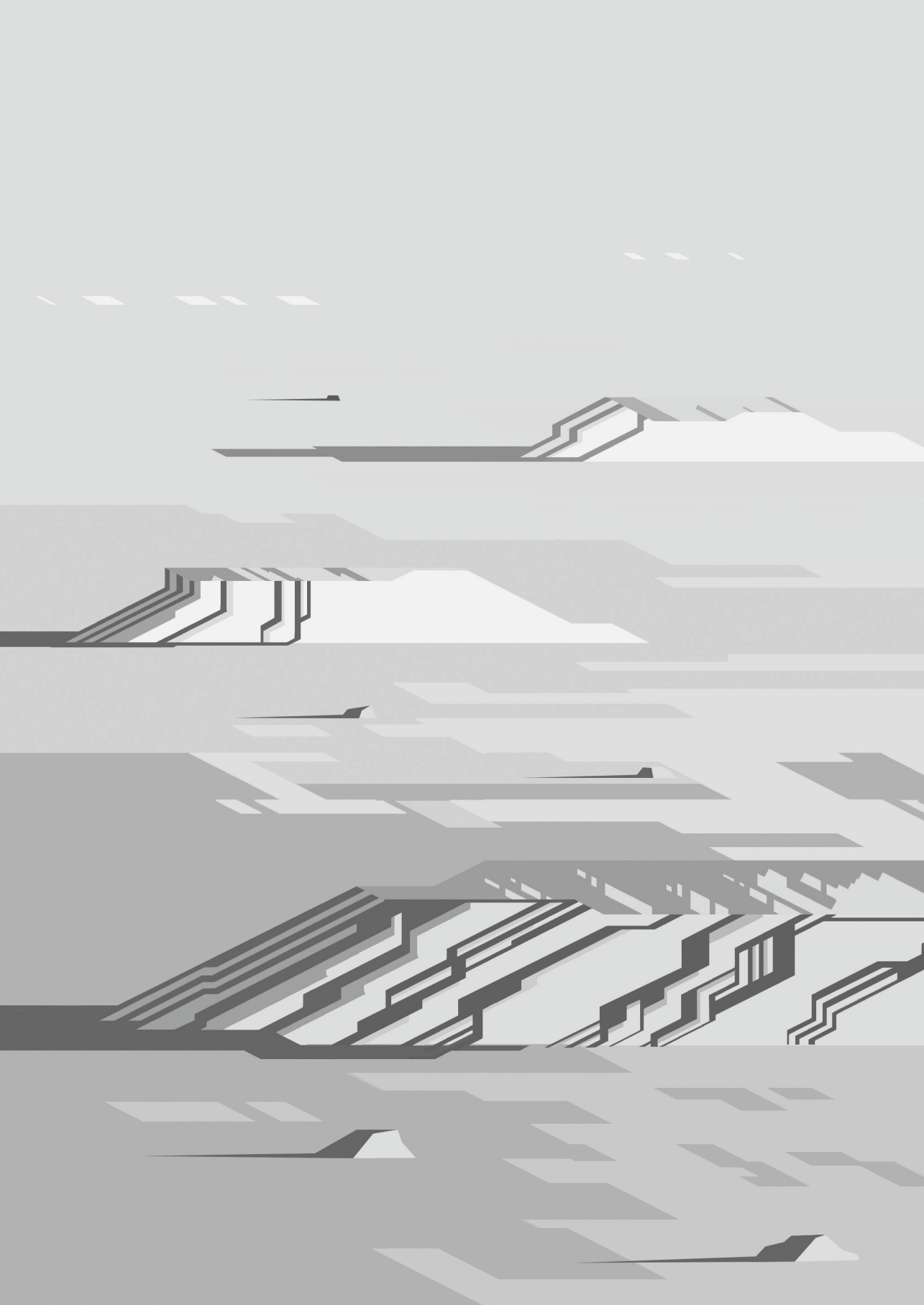
Parameter	Value	Range deterministic sensitivity analysis (-20%; +20%)	Beta distribution probabilistic sensitivity analysis (alpha; beta)
Transitions (3 monthly probability)			
Relapse after withdrawal of anti-TNF			
Year 1	0.064	0.051 – 0.077	31; 450
Year 2	0.036	0.029 – 0.043	10; 277
Year 3-5	0.027	0.021 – 0.032	1.8; 67
Remission after reintroduction of anti-TNF	0.67	0.536 – 0.804	193; 95
LOR to reintroduced anti-TNF	0.035	0.028 – 0.041	2.1; 57.9
Remission after dose-escalation (after reintroduction anti-TNF)	0.30	0.242 – 0.364	12; 28
Clinical response to tofacitinib	0.58	0.461 – 0.691	633; 467
LOR to tofacitinib	0.09	0.073 – 0.109	6.1; 61.9
Clinical response to vedolizumab	0.56	0.448 – 0.672	268.2; 210.7
LOR to vedolizumab	0.014	0.011 – 0.017	16.2; 105.8
Clinical response to 2nd anti-TNF	0.41	0.328 – 0.492	123 ; 177
LOR to 2nd anti-TNF	0.22	0.179 – 0.269	25.3; 87.7
Clinical response to ustekinumab LOR to ustekinumab	0.62 0.11	0.494 – 0.742 0.086 – 0.129	199; 123 18.5; 153.5
LOR to anti-TNF	0.017	0.014 – 0.021	1.5; 83.5
Clinical response to dose-escalation	0.60	0.483 – 0.724	213; 140
LOR dose-escalated anti-TNF	0.066	0.053 – 0.079	5.9; 84.0
Perioperative mortality (colectomy)	0,012	Fixed	69; 5879
Utilities			
Remission	0.87	0.70 – 1.04	4.9; 0.7
Mild	0.76	0.61 – 0.91	6.7; 2.1
Moderate-severe	0.41	0.33 – 0.49	4.7; 6.8
Ileostomy	0.72	0.58 – 0.86	1.5; 0.6

Supplementary Figure 1. Illustrations of probabilistic sensitivity analyses with 1000 Monte Carlo simulations altering transition probabilities and utility weights. A) Cost-effectiveness plane B) Incremental cost-effectiveness plane. C) Cost-effectiveness plane when utility weights are kept constant. D) Incremental cost-effectiveness plane when utility weights are kept constant.



Supplementary Figure 2. Minimal requirements for a risk-stratified protocol for withdrawal of anti-TNF in ulcerative colitis to be more cost-effective than withdrawal of anti-TNF in all patients





CHAPTER 3

Complete endoscopic healing is associated with a lower relapse risk after anti-TNF withdrawal in inflammatory bowel disease

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Clin Gastroenterol Hepatol. 2022 Aug 31;S1542-3565(22)00820-5.

Abstract

Introduction

Discontinuation of anti-tumor necrosis factor-α treatment (anti-TNF; infliximab and adalimumab) in patients with inflammatory bowel disease (IBD) is associated with a high relapse risk which may be influenced by endoscopic activity at the time of stopping. We assessed the relapse rate after anti-TNF withdrawal in patients with endoscopic healing, and studied predictors of relapse including the depth of endoscopic healing.

Methods

This was a multicenter, prospective study in adult patients with Crohn's disease (CD), ulcerative colitis (UC) or IBD-unclassified (IBDU), with ≥6 months of corticosteroid-free clinical remission (confirmed at baseline) and endoscopic healing (Mayo<2/SES-CD<5 without large ulcers), who discontinued anti-TNF between 2018-2020 in the Netherlands. We performed Kaplan-Meier and Cox regression analyses to assess the relapse rate and evaluate potential predictors: partial (Mayo 1/SES-CD 3-4) versus complete (Mayo 0/SES-CD 0-2) endoscopic healing, anti-TNF trough levels and immunomodulator and/or mesalamine use.

Results

Among 81 patients (CD: n=41, 51%), with a median follow-up of 2.0 (IQR 1.6-2.1) years, 40 (49%) patients relapsed. Relapse rates in CD and UC/IBDU patients were comparable. At 12 months, 70% versus 35% of patients with partial versus complete endoscopic healing relapsed, respectively (adjusted hazard rate [aHR]: 3.28, 95%CI: 1.43-7.50). Mesalamine use was associated with fewer relapses in UC/IBDU patients (aHR 0.08, 95%CI 0.01-0.67). Thirty patients restarted anti-TNF, and clinical remission was regained in 73% at 3 months.

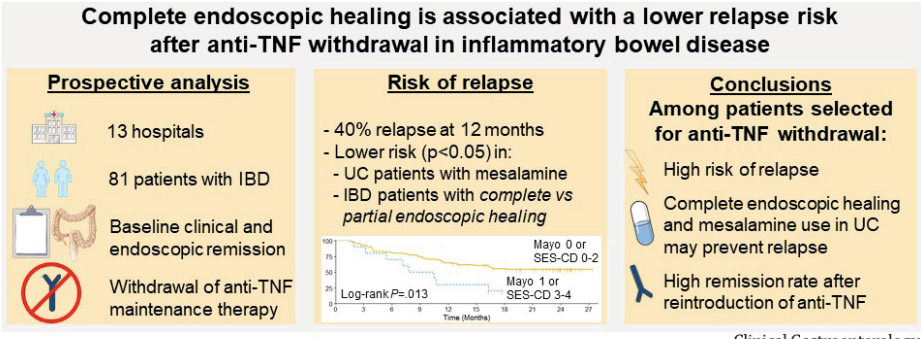
Conclusion

The relapse risk was high after anti-TNF withdrawal in IBD patients with endoscopic healing, but remission was regained in most cases after anti-TNF reintroduction. Complete endoscopic healing, and mesalamine treatment in UC/IBDU patients, decreased the risk of relapse.

Keywords

De-escalation, endoscopic remission, biologicals, deep remission

Graphical Abstract



Clinical Gastroenterology and Hepatology

Introduction

De-escalation of anti-tumor necrosis factor-α (anti-TNF) treatment in patients with inflammatory bowel disease (IBD) in remission can potentially reduce side effects, including risks of serious infections and malignancies, decrease health care expenditures, and meet patients' preferences.[1–3] Data from randomized-controlled trials (RCTs) have proven that anti-TNF withdrawal considerably increases the risk of relapse, both in ulcerative colitis (UC) and Crohn's disease (CD).[4,5] Prospective studies and a meta-analysis have estimated that approximately 30-45% of patients relapse at 12 months, while reintroduction of anti-TNF therapy restores remission in more than 80% of patients.[4–7] Currently, no consensus exists on patient selection for treatment de-escalation.[8,9]

Emerging evidence suggests that persistent inflammation compromises treatment outcomes in asymptomatic patients with IBD, when assessed endoscopically, histologically or with fecal calprotectin.[10–14] A prior study suggests that the depth of endoscopic healing influences the rate of biological failure as well as long-term outcomes (hospitalizations and surgeries) in patients with CD.[13] In the context of de-escalation from anti-TNF therapy, the risk of relapse was lower in IBD patients with endoscopic healing in addition to clinical remission,[6,15,16] but it remains unclear which degree of endoscopic healing is needed to lower the risk of relapse.

We conducted a multicenter, prospective study in IBD patients in clinical remission and with endoscopic healing in whom anti-TNF treatment was discontinued. We aimed to assess the relapse rate, evaluate predictors of relapse including the degree of endoscopic healing, and study outcomes after reintroduction of anti-TNF therapy.

Methods

Study design and population

This was a prospective observational study in 2 tertiary referral centers and 11 general hospitals in the Netherlands. Patients were recruited between 2018-2020. Inclusion criteria were a diagnosis of CD, UC or IBD-unclassified (IBDU), age ≥18 years, ≥6 months of corticosteroid-free clinical remission with infliximab or adalimumab, confirmed baseline clinical remission and endoscopic healing (as defined below), elective discontinuation of anti-TNF therapy (without starting another biological or tofacitinib), no current hospitalization and no (intended) pregnancy. Withdrawal of anti-TNF treatment was discussed in a shared decision-making process between the patient and treating physician as part of usual care in which the risks versus benefits of discontinuing treatment while in confirmed remission were discussed, in accordance with the Dutch IBD treatment guideline.[17] Patients who opted to discontinue anti-TNF were offered to voluntarily participate in this observational study.

Study Procedures

Baseline measurements included fecal calprotectin, C-reactive protein (CRP), anti-TNF trough levels, and endoscopic evaluation of disease activity. Patients could continue or start mesalamine or immunomodulator (thiopurine or methotrexate) treatment at the discretion of the treating physician.

The follow-up started at the last administration of anti-TNF treatment. Recommended monitoring included measurements of CRP and fecal calprotectin at 3,6,12 and 24 months, and an endoscopy at 12 months. In case of a (suspected) relapse, endoscopy and measurements of CRP and fecal calprotectin were recommended. The preferred treatment at relapse was reintroduction of the anti-TNF agent. After a relapse, monitoring included CRP, fecal calprotectin and an anti-TNF trough level at 3 months.

Participants received questionnaires by email at 0,3,6,12 and 24 months of follow-up, at the time of a relapse and 3 months thereafter. Questionnaires included the patient-Harvey Bradshaw Index (HBI) for CD patients or patient-Simple Clinical Colitis Activity Index (SCCAI) for UC and IBDU patients, and the short IBD Quality of Life questionnaire (SIBDQ; used under license from McMaster University, Hamilton, Canada).[18–20] General well-being was scored on a scale ranging 1-10. In addition, patients received a non-validated patient perspective questionnaire at 0,12 and 24 months, in which all items were scored on a visual analogue scale ranging 1-10 (**Supplementary Table 1**).

Data collection and definitions

Clinical data were collected from the electronic health records at each visit, including the physician global assessment (PGA; remission versus active IBD), IBD-related medication, laboratory parameters, radiological examinations, endoscopic and surgical procedures, and hospitalizations. No central reading or assessments were performed.

Clinical remission was defined as a SCCAI/HBI <5, biochemical remission was defined as CRP <10mg/L and fecal calprotectin <250µg/g, and endoscopic healing was defined as an endoscopic Mayo score <2 or Simple Endoscopic Score for CD (SES-CD) <5 without large ulcers. Endoscopic healing was sub-classified as complete endoscopic healing (Mayo 0/ SES-CD 0-2) versus partial endoscopic healing (Mayo 1/SES-CD 3-4).[10]

Clinical relapse was defined as a SCCAI/HBI ≥5 with ≥3 points increase from baseline. Biochemical and endoscopic relapse were defined as absence of previously defined biochemical remission and endoscopic healing, respectively.

Trough levels <3mg/L for infliximab and <5mg/L for adalimumab were considered subtherapeutic. At most participating sites, anti-drug antibodies were only measured in case of trough levels <1.0mg/L.

Outcomes

The primary composite outcome was "relapse", defined as any of the following: endoscopic relapse, clinical and biochemical relapse, step-up of medical therapy (any treatment for active IBD, including steroids and topical therapy, excluding antibiotics), IBD-related hospitalization or surgery, or newly diagnosed intestinal stenotic disease, (perianal) abscess or fistula.

Secondary outcomes included (the degree of) endoscopic relapse, IBD-related hospitalizations and surgeries, potential predictors of relapse and effectiveness of reintroduction of anti-TNF treatment after 3 months.

Statistical analysis

All data were censored on October 1st, 2021 – at which point all patients had ≥1 year of follow-up.

Baseline characteristics were described as frequencies (with % of patients without missing data), or median (interquartile range [IQR]) and compared with Chi-Square tests or Mann-Whitney U test, respectively. Time to relapse was analyzed using Kaplan-Meier curves with log-rank tests for significance.

Subtherapeutic trough levels, complete versus partial endoscopic healing, and immunomodulator and/or mesalamine use were assessed as potential predictors of relapse, employing Cox regression analysis. The proportional hazards assumption was confirmed using Schoenfeld residuals, missing trough levels were replaced employing multiple imputation, and study site was entered as a random effect on the baseline hazard. All covariates were selected *a priori* and directly entered in the multivariable model. Stratified analyses were conducted for patients with CD versus UC/IBDU. A sensitivity analysis was performed excluding patients with partial endoscopic healing. An exploratory post-hoc univariable analysis was conducted for other clinically relevant potential predictors of relapse.

Pairwise comparisons (including pre- versus post-withdrawal trough levels) between time points in one individual were assessed with Wilcoxon signed-rank test. If trough levels were measured repeatedly after reintroduction of anti-TNF, the lowest serum concentration was analyzed. SIBDQ and well-being scores were analyzed using an unadjusted linear mixed model.

Other repeated measurements (PGA, fecal calprotectin, CRP and HBI/SCCAI) were analyzed descriptively. Measurements were performed as part of routine care, and not always at the exact predefined time points. We therefore clustered measurements in 3-monthly intervals (one month before, two months after the predefined time point). If multiple measurements were performed in one interval, the value most indicative of active disease was analyzed.

Study Oversight

All patients provided written informed consent. This study received exempt status from the Institutional Review Board of the University Medical Center Utrecht due to its observational design.

Results

Population

We enrolled 81 patients (CD: n=41, 51%; **Supplementary Figure 1**). At baseline, the median duration of remission was 3.5 (IQR 2.0-4.9) years (**Table 1**). The median disease duration was 9.1 years (IQR 4.5-14.3). All patients had endoscopic healing (Mayo<2/SES-CD<5 without large ulcers), and 71 (88%) patients met the strict criteria for complete endoscopic healing (Mayo 0/SES-CD 0-2). Anti-TNF trough levels were subtherapeutic in 24 (34%) patients (**Table 2**). Four (4.9%) patients had previously experienced primary non-response or loss of response to anti-TNF or vedolizumab (**Table 1**). Following anti-TNF withdrawal, 21 (25.9%) patients continued immunomodulators, which was similar between patients discontinuing adalimumab versus infliximab (n=6, 27% versus n=15, 25%, respectively; p=0.87). The median follow-up time was 2.0 years (IQR 1.6-2.1).

Table 1. Baseline characteristics

	All patients (n=81)	**UC/IBDU (n=40)**	**CD (n=41)**
Age, years	40.2 (29.7 – 53.1)	45.1 (32.2 – 52.7)	34.3 (28.7 – 54.4)
Female sex	42 (51.9)	18 (45.0)	24 (58.5)
Body mass index (BMI), kg/m^2	24.1 (22.5 – 26.8)	23.8 (22.4 – 25.5)	25.2 (22.5 – 27.7)
Smoking	7 (8.6)	3 (7.5)	4 (9.8)
Age at diagnosis, years <18 years 18-40 years ≥40 years	28.5 (22.1 – 37.5) 6 (7.4) 57 (70.4) 18 (19.5)	30.5 (23.1 – 40.1) 2 (5.0) 28 (70.0) 10 (25.0)	25.9 (21.2 – 36.8) 4 (9.8) 29 (70.7) 18 (22.2)
Disease duration, years	9.1 (4.5 – 14.3)	10.0 (7.7 – 12.9)	5.5 (4.0 – 14.9)
Duration of remission, years	3.5 (2.0 – 4.9)	3.6 (2.4 – 5.2)	3.3 (1.9 – 4.8)
Duration of anti-TNF treatment, years	4.2 (2.6 – 8.0)	4.3 (2.8 – 6.9)	4.2 (2.6 – 8.0)
Infliximab (versus adalimumab)	59 (72.8)	32 (80.0)	27 (65.9)
IBD-U	1 (1.2)	1 (2.5)	-
UC/IBDU extent E1 Proctitis E2 Left-sided E3 Extensive	- - -	 3 (7.5) 14 (35.0) 23 (57.5)	- - -

Table 1. Baseline characteristics (continued)

	All patients (n=81)	UC/IBDU (n=40)	CD (n=41)
Disease location	-	-	
L1 Ileum	-	-	5 (12.2)
L2 Colon	-	-	14 (34.1)
L3 Ileocolonic	-	-	22 (53.7)
L1/2/3 + L4 Upper GI			2 (4.9)
Disease behavior	-	-	30 (73.2)
B1 inflammatory	-	-	7 (17.1)
B2 stricture	-	-	4 (9.8)
B3 penetrating			
Perianal disease	-	-	8 (19.5)
anti-TNF (also) for perianal fistula	-	-	3 (7.5)
Prior anti-TNF exposure	12 (14.8)	9 (22.5)	3 (7.3)
Stopped for primary non-response	2 (2.5)	2 (5.0)	-
Stopped for loss of response	1 (1.2)	1 (2.5)	-
Stopped as de-escalation	3 (3.7)	3 (7.5)	-
Stopped for side effects	6 (7.4)	3 (7.5)	3 (7.3)
Prior medication exposure			
Systemic steroids	71 (87.7)	40 (100)	31 (75.6)
Thiopurines	74 (91.4)	37 (92.5)	37 (90.2)
Methotrexate	10 (12.3)	1 (2.5)	9 (22.0)
Immunomodulator failure before anti-TNF	45 (56.3)	21 (52.5)	24 (60)
Vedolizumab	1 (1.2)	1 (2.5)	-
Concomitant immunomodulator at the start of anti-TNF therapy	58 (72.5)	31 (77.5)	27 (67.5)
Treatment after anti-TNF withdrawal	16 (19.8)	14 (35.0)	2 (4.9)
Mesalamine[1]	21 (25.9)	10 (25.0)	11 (26.8)
Immunomodulator[2]	3 (3.7)	2 (5.0)	1 (2.4)
Rectal therapy	44 (54.3)	17 (42.5)	27 (65.9)
None			

Presented as number (%) or median (interquartile range). Missing data: BMI (n=1), immunomodulator failure/concomitant immunomodulator at the start of anti-TNF (n=1).1) Started at baseline (n=7). 2) Started at baseline (n=5).

Table 2. Baseline diagnostic assessment

	All patients (n=81)	UC/IBDU (n=40)	CD (n=41)
SCCAI or HBI score	-	0 (0 – 1)	2 (1 – 3)
SIBDQ score	61 (54 – 64)	61 (56 – 66)	58 (51 – 63)
CRP (mg/L)	0 (0 – 2.1)	0 (0 – 1.1)	0.8 (0 – 3.1)
<10mg/L, n (%)	78 (97.5)	38 (95.0)	40 (100)
Fecal calprotectin (µg/g)	11 (0 – 47)	9 (0 – 31.5)	14.5 (6 – 56.8)
<250µg/g, n (%)	74 (96.1)	39 (100)	35 (92.1)
Endoscopic healing			
Complete (SES-CD 0-2/eMayo 0)	71 (87.7)	37 (92.5)	34 (82.9)
Partial (SES-CD 3-4 / Mayo 1)	10 (12.3)	3 (7.5)	7 (17.1)
Anti-TNF trough levels			
Adalimumab (mg/L)	8 (4.6 – 11.8)	10.3 (3.0 – 15.8)	7.4 (4.7 – 10.7)
Infliximab (mg/L)	4 (2.0 – 6.0)	5.6 (3.1 – 7.7)	3.3 (0.2 – 5.0)
Subtherapeutic (n, %)	24 (33.8)	9 (26.5)	15 (40.5)
Undetectable (n, %)	9 (12.3)	1 (2.9)	8 (20.5)
Anti-drug antibodies detected	8 (19.5)	1 (2.5)	7 (17.1)
Not present	14 (17.3)	10 (25.0)	4 (9.8)
Not measured	59 (72.8)	29 (72.5)	30 (73.2)
Antibody titer (AU/mL)	145 (82 – 408)	110 (-)	180 (65 – 565)
Thiopurine metabolites[1]			
6-thioguanine nucleotides (6-TGN, pmol/8*10^8 red blood cells)	516 (368 – 582)	382 (255 – 520)	557 (453 – 654)
6-methylmercaptopurine (6-MMP, pmol/8*10^8 red blood cells)	326 (238 – 448)	203 (173 – 300)	369 (320 – 1288)

Presented as number (%) or median (interquartile range).1) For 16 patients using baseline thiopurine, excluding those who started at baseline (n=5). Missing data: CRP (n=1), fecal calprotectin (n=4), infliximab trough level (n=7), adalimumab trough level (n=3), 6TGN (n=4), 6mmp (n=5).

Risk of relapse

During follow-up, 40 (49%) of patients relapsed. Relapse rates were 7%, 21%, 28% and 40% at 3,6,9 and 12 months, respectively (**Figure 1a**). The relapse was confirmed with endoscopy, fecal calprotectin or CRP in 33 (83%) cases, while 7 (17%) were declared based on treatment escalation for a clinical flare. The relapse rate at 12 months was comparable between patients with UC/IBDU (n=17, 43%) and CD (n=15, 37%; **Figure 1b,** p=0.76), and between patients discontinuing adalimumab (n=8, 36%) and infliximab (n=24, 41%; data not shown, p=0.96).

Partial endoscopic healing (Mayo 1/SES-CD 3-4) was independently associated with a higher relapse risk (aHR 3.28, 95%CI 1.43-7.50) compared to complete endoscopic healing (Mayo 0/SES-CD 0-2), and this remained significant in the stratified analyses for patients with UC/

IBDU and CD (**Table 3**). At 12 months, 7 (70%) of patients with partial endoscopic healing had relapsed, compared with 25 (35%) patients with complete endoscopic healing (**Figure 1C)**. Of note, the time between the baseline endoscopy and withdrawal of anti-TNF (<6 months in 77 [95%] of patients) did not significantly affect the hazard ratio for partial versus complete endoscopic healing (**Supplementary Table 2**).

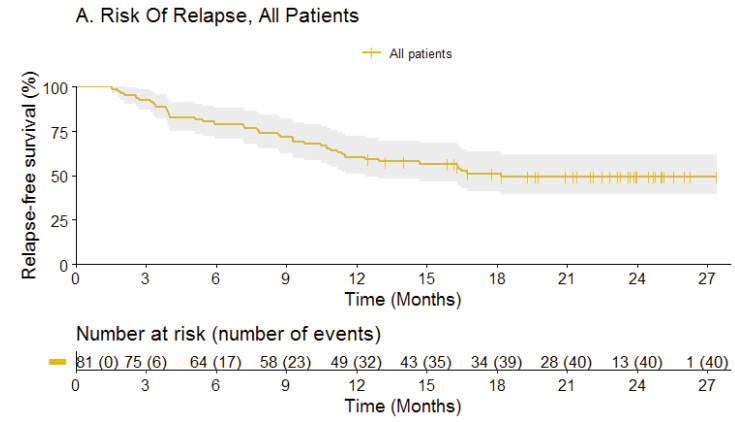
Mesalamine treatment was independently associated with a decreased risk of relapse in patients with UC/IBDU (aHR 0.08, 95%CI 0.01-0.67, **Figure 1d** and **Table 3**), or patients with UC only (aHR 0.08, 95%CI 0.01-0.71). Subtherapeutic anti-TNF trough levels and immunomodulator use were not associated with the risk of relapse (**Figure 1e-f)**. No relevant changes to the hazard ratios for immunomodulators, mesalamine and trough levels were observed in the sensitivity analysis excluding patients with partial endoscopic healing (**Supplementary Table 3**). No other potential predictors for relapse were identified in the exploratory post-hoc analysis (**Supplementary Table 4**).

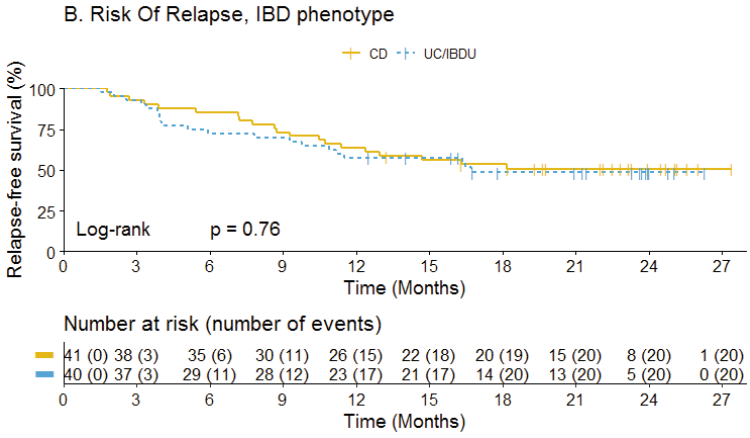
Table 3. Predictors of relapse, multivariable Cox regression analysis.

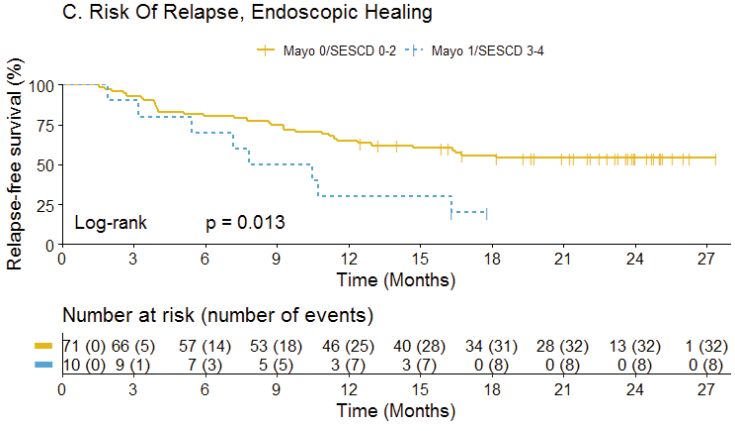
	All patients aHR (95%CI)	**P**	**CD patients aHR (95%CI)**	**P**	**UC/IBDU patients aHR (95%CI)**	**P**
Subtherapeutic anti-TNF trough level	0.61 (0.30 – 1.23)	0.16	0.61 (0.24 – 1.54)	0.30	1.26 (0.36 – 4.37)	0.71
Partial (versus complete) endoscopic healing	3.28 (1.43 – 7.50)	0.005*	4.16 (1.47 – 11.8)	0.007*	11.7 (1.02 – 133.4)	0.05*
Immunomodulator use	1.05 (0.50 – 2.18)	0.90	2.06 (0.76 – 5.57)	0.15	0.46 (0.14 – 1.52)	0.20
Mesalamine use	0.27 (0.08 – 0.88)	0.03*	-	-	0.08 (0.01 – 0.67)	0.02*

*Significant at p<0.05. aHR: adjusted hazard ratio.

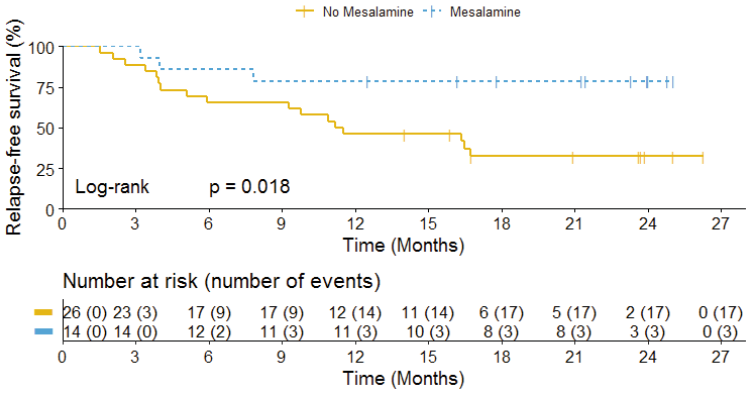
Figure 1. Relapse after anti-TNF withdrawal, Kaplan-Meier estimates A) All patients B) CD versus UC/IBDU C) Endoscopic healing D) Mesalamine use in UC/IBDU patients, E) anti-TNF trough levels, F) Immunomodulator use.



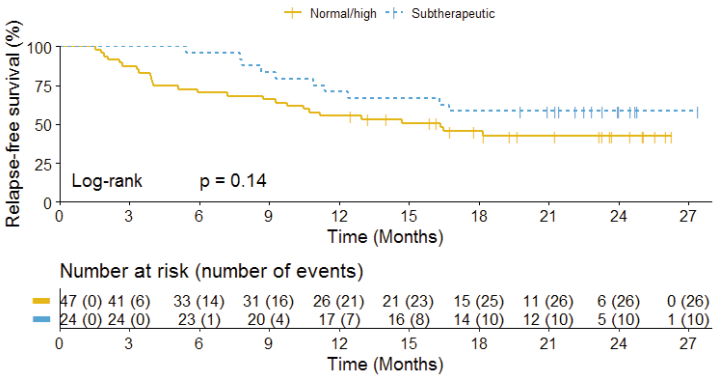




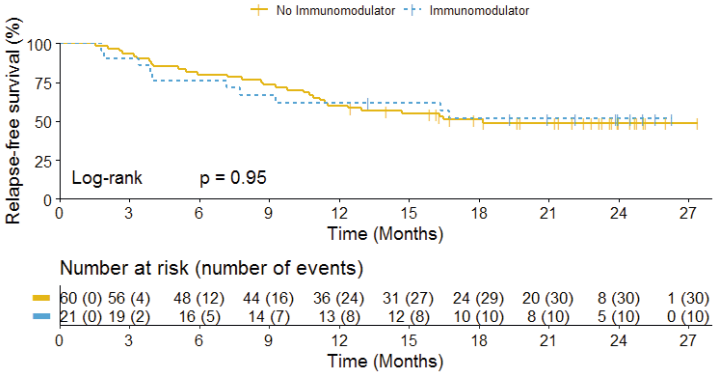
D. Risk Of Relapse, Mesalamine treatment (UC/IBDU)



E. Risk Of Relapse, Anti-TNF Trough Levels



F. Risk Of Relapse, Immunomodulator Treatment

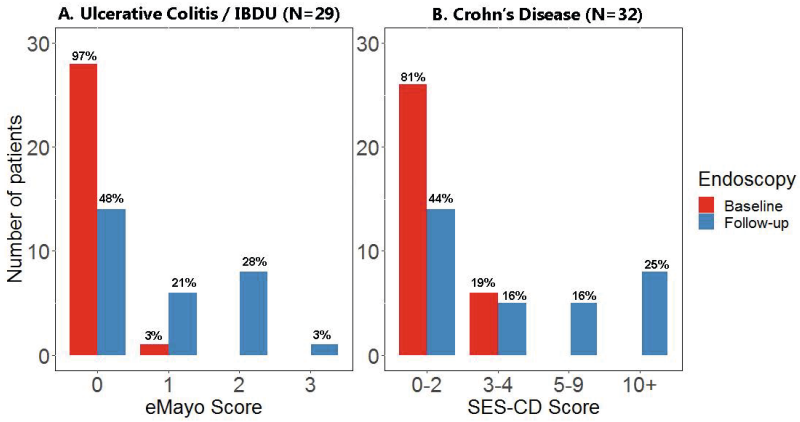


Secondary outcomes

A follow-up endoscopy was available in 29 (73%) patients with UC/IBDU and 32 (78%) patients with CD, after a median of 1.1 years (IQR 0.9-1.2). The number of patients with complete endoscopic healing decreased considerably both in UC (from 28 [97%] to 14 [48%] and CD (from 26 [81%] to 14 [44%]; **Figure 2**).

Other secondary outcomes are presented in **Supplementary Table 5**. Notably, 3 (4%) patients were hospitalized for active IBD and one patient with CD (2%) underwent an ileocecal resection for a symptomatic stenosis.

Figure 2. Endoscopic outcomes of patients with an available follow-up endoscopy (n=61, performed after a median of 1.1 years).



Anti-TNF reintroduction

After relapse, 30 patients (75%) restarted anti-TNF treatment (of whom one withdrew consent for further follow-up), 3 (8%) started vedolizumab and 7 (18%) did not (re)start a biological or tofacitinib during the study period.

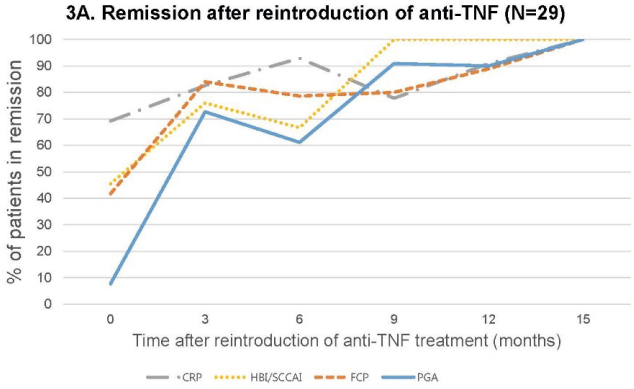
Most patients (n=26, 87%) restarted the same anti-TNF agent. Adalimumab (n=10, 33%) or infliximab (n=20, 66%) was (re)started after a median of 0.9 (IQR 0.4-1.2) years since withdrawal of treatment, and 24 days (IQR 10-50) since the onset of the relapse. A concomitant immunomodulator was started or continued in 12 (40%) patients.

After reintroduction of anti-TNF treatment, 73% and 90% of patients were in remission at 3 and 12 months, respectively, based on the PGA. The remission rate at 3 months did not differ between patients restarting anti-TNF monotherapy or combination therapy (77% versus 67%, respectively; p=0.60). Remission rates based on CRP, fecal calprotectin, HBI/SCCAI were similar (**Figure 3A**). During a median follow-up of 1.0 (IQR 0.7-1.6) year after

reintroduction of anti-TNF treatment, 4 (14%) patients discontinued therapy **(Figure 3B)** due to primary non-response (n=2) or incomplete response (n=2).

Trough levels and/or anti-drug antibodies were measured at least once in 27 (93%) patients after restarting treatment. Pre-withdrawal trough levels were similar to those after reintroduction of infliximab (median of 5.4 versus 4.6mg/L, p=0.53, n=14), or adalimumab (8.3 versus 8.1mg/L, p=1.00, n=6) among patients who restarted the same compound. Anti-drug antibodies were detected in 3 (10%) patients, of whom one used concomitant thiopurine.

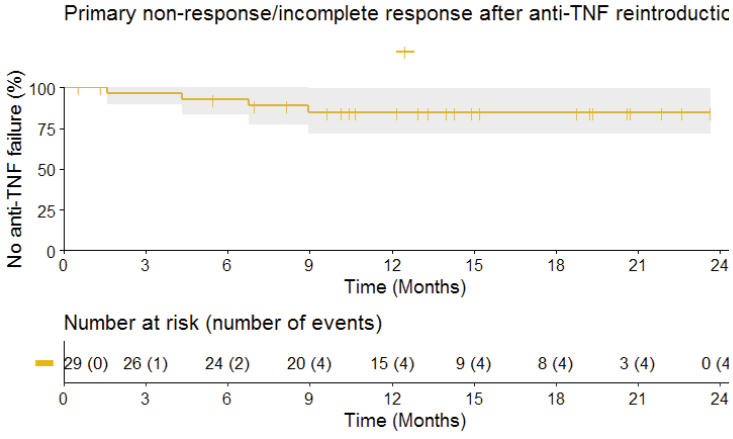
Figure 3A. Outcomes after anti-TNF reintroduction. A) Remission after starting anti-TNF, based on CRP>10mg/L, HBI/SCCAI<5, fecal calprotectin(FCP)<250µg/g and physician global assessment.



Data availability

Patients at risk	29	26	25	22	15	12
PGA	26	22	18	11	10	11
FCP	24	25	14	10	9	9
CRP	26	23	14	9	11	11
HBI/SCCAI	22	25	6	9	5	10

Figure 3B. Outcomes after anti-TNF reintroduction. B) Discontinuation of anti-TNF after reintroduction due to primary non-response/incomplete response.



Patient perspective

Baseline perceptions and future expectations regarding IBD-symptoms and anti-TNF treatment were similar between patients who relapsed during follow-up, compared with patients with sustained remission (**Supplementary Table 1**). Stopping anti-TNF treatment was generally considered a good decision (median score of 9/10 at 12 months, and 8/10 at 24 months), although patients who had relapsed were less satisfied with the decision (median score of 5/10 both at 12 and 24 months), and reported more symptoms (**Supplementary Table 1**).

General well-being and SIBDQ scores remained stable over the entire follow-up and did not differ between patients with relapse versus without relapse on a population level (**Supplementary Figure 2**). However, among individual patients who relapsed, SIBDQ scores and general well-being (available in 85%) were significantly higher at baseline compared with the time point of relapse (SIBDQ: 62 [IQR 56-66] at baseline versus 49 [IQR 41-57] at relapse, p<0.001; well-being: 9 [IQR 8-10] versus 6 [IQR 5-7], p<0.001). Reintroduction of anti-TNF treatment restored quality of life and well-being (available in 66%) within three months (SIBDQ from 50 [IQR: 41-54] at anti-TNF reintroduction to 56 ([IQR 52-65] three months after reintroduction, p=0.003; well-being from 6 [IQR 4-7] to 8 [IQR 7-8], p=0.001).

Discussion

In this prospective, multicenter study looking at withdrawal of anti-TNF therapy, the risk of relapse was high (40% at 12 months), despite a careful selection of patients with IBD in clinical remission and with endoscopic healing. Complete endoscopic healing (Mayo 0/ SES-CD 0-2) was associated with a significantly lower risk of relapse. Mesalamine treatment was associated with a lower relapse risk in patients with UC or IBDU, but no protective effect of continuing treatment with immunomodulators could be detected. Reintroduction of anti-TNF therapy re-established remission in 73% of patients at three months.

Recent RCTs confirmed that withdrawal of anti-TNF considerably increases the risk of relapse both in UC and CD.[4,5] The observed relapse rate of 40% at one year in this study is in line with prior prospective studies – even though endoscopic healing was a prerequisite for anti-TNF withdrawal.[4–6] Of note, this is much higher than the risk of loss of response (4.8% per patient-year) among patients who continued anti-TNF therapy after a similar duration of treatment in a retrospective study performed at our centers.[21]

The main result of this study was that the risk of relapse was lower among patients with *complete* endoscopic healing, compared with *partial* endoscopic healing (70% versus 35% at 12 months). This large difference underscores the clinical importance of this finding. In the STORI trial, CD patients with complete endoscopic healing (CDEIS 0) were also at lower risk of relapse after withdrawal of infliximab, but this was compared with all other participants, including those without endoscopic healing.[6] Among UC patients who discontinued

infliximab in a recent RCT, complete endoscopic healing (Mayo 0 versus 1) was not associated with a decreased risk of relapse. However, a trend was observed for a lower risk in patients with histologic healing, supporting the concept of applying stringent remission criteria prior to withdrawal of anti-TNF therapy.[5] In retrospective studies, endoscopic healing was not associated with a lower risk of relapse in studies including both patients with CD and UC.[22,23] This may be attributed to the non-standardized criteria used in these studies and lack of patients without endoscopic healing for comparison.

Continuing mesalamine treatment after de-escalation of anti-TNF therapy reduced the risk of relapse in patients with UC/IBDU, but continuation of immunomodulators and subtherapeutic trough levels did not affect the relapse risk in this study. Our finding regarding mesalamine is promising, but should be interpreted with caution, given contradictory findings in a retrospective study in which UC patients continuing mesalamine after anti-TNF withdrawal had a higher relapse rate than those continuing immunomodulators.[24] A protective effect of continuing immunomodulators after anti-TNF withdrawal was established in a prior individual patient data meta-analysis with 1317 patients with CD.[25] Only one small retrospective study (n=18) found a protective effect of immunomodulators in UC after anti-TNF withdrawal,[26] while other (larger) studies did not.[5,23,27] It is unknown why immunomodulators were not associated with a lower relapse risk in the present study. Unlike in prior studies, few (25.9%) patients continued immunomodulators after anti-TNF withdrawal, perhaps because most patients had failed immunomodulators prior to starting anti-TNF therapy. Moreover, for both mesalamine and immunomodulator use, selection bias may also have occurred as the decision to continue or start these agents was left to the treating physician. Interestingly, prior studies reported a protective effect of subtherapeutic pre-withdrawal anti-TNF trough levels.[6,28] In our study, this was not statistically significant, which can be the result of missing trough levels (12%) and limited sample size.

Reintroduction of anti-TNF agents after a relapse restored remission in 73% of patients within 3 months, in line with previous studies.[7] Furthermore, patient-reported quality of life (SIBDQ) and general well-being declined at the time of relapse, but was restored with reintroduction of treatment. As a result, quality of life and general well-being were similar between patients who relapsed versus those who maintained remission, when considering the entire follow-up on a population level. Similarly, in the randomized-controlled SPARE trial, CD patients discontinuing infliximab with reintroduction upon relapse spent only 6 or 14 days less in remission over the course of 2 years, compared with patients continuing combination therapy or stopping the immunomodulator, respectively.[4] This underscores the feasibility of a strategy combining withdrawal of anti-TNF treatment with reintroduction upon relapse.

Our findings are based on a selected cohort of patients with IBD in confirmed clinical remission and with endoscopic healing, with detailed clinical, pharmacokinetic and endoscopic data as well as patient-reported outcomes. Nevertheless, we acknowledge

some limitations. Although our sample size was relatively large for a prospective study with endoscopic data, few patients in our study had partial endoscopic healing (n=10, 12%), resulting in wide confidence intervals for this parameter. Ideally, larger prospective studies should confirm the importance of complete endoscopic healing and should also assess histological remission, especially in UC.[5] A longer follow-up may be needed to detect major complications after withdrawal of anti-TNF treatment (e.g. need for surgery).[29] De-escalation of anti-TNF therapy is performed exclusively in a highly selected patient group with stable remission (6.9% of patients using anti-TNF maintenance therapy in a prior retrospective study).[21] Consequently, few patients with an unfavorable IBD phenotype, such as stricturing or penetrating CD, anti-TNF for perianal fistulizing CD, young age at diagnosis, or prior biological failure, were included in this study. Therefore, our findings may not be generalizable to patients with a more severe IBD phenotype.

In conclusion, among selected patients with IBD in clinical remission and with endoscopic healing, the risk of relapse after withdrawal of anti-TNF therapy remained high, but reintroduction of anti-TNF treatment was successful in most cases. Applying strict criteria for endoscopic healing, and mesalamine treatment for patients with UC or IBDU, may lower the risk of relapse after withdrawal of anti-TNF treatment.

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Supplementary Table 1. Patient perspective questionnaire

	All patients (n=81)	No relapse (n=41)	Relapse (n=40)	P
Baseline[1]	**N=81**	**N=41**	**N=40**	
Before I started anti-TNF treatment, my IBD symptoms were very severe	9 (8 – 10)	9 (8 – 10)	9 (7 – 9)	0.46
While being treated with anti-TNF in the past year, I did not experience any IBD-related symptoms	9 (7 – 10)	9 (7 – 10)	9 (8 – 10)	0.12
I worry that if I stop anti-TNF treatment, I will experience more IBD-related symptoms	5 (4 – 7)	5 (4 – 7)	5 (4 – 6)	0.53
I'm experiencing many side effects from anti-TNF treatment	3 (1 – 6)	3 (1 – 6)	2 (1 – 6)	0.21
I worry about future side effects of anti-TNF treatment	3 (1 – 6)	2 (1 – 5)	4 (1 – 6)	0.65
Anti-TNF administration (going to the hospital for an infusion, self-administration in the skin) is burdensome or uncomfortable to me	1 (1 – 2)	1 (1 – 2)	2 (1 – 3)	0.52
Anti-TNF is a very effective treatment for my Crohn's disease/ulcerative colitis	10 (9 – 10)	10 (8 – 10)	10 (9 – 10)	0.51
I would like to stop anti-TNF treatment	10 (7 – 10)	10 (8 – 10)	9 (6 – 10)	0.10
12-month follow-up[1]	**N=74**	**N=44**	**N=30**	
In the past year, I did not experience any IBD-related symptoms	7 (3 – 9)	9 (7 – 10)	3 (2 – 5)	<0.001*
In the past year, I experienced fewer IBD-related symptoms than the year before	5 (2 – 9)	7 (4 – 10)	3 (1 – 5)	0.001*
Stopping anti-TNF treatment was a good decision	10 (5 – 10)	10 (10 – 10)	5 (2 – 7)	<0.001*
24 month follow-up[1]	**N=40**	**N=19**	**N=21**	
In the past year, I did not experience any IBD-related symptoms	7 (4 – 9)	8 (6 – 9)	7 (3 – 8)	0.10
In the past year, I experienced fewer IBD-related symptoms than the year before	8 (5 – 10)	8 (5 – 10)	8 (3 – 10)	0.79
Stopping anti-TNF treatment was a good decision	9 (5 – 10)	10 (9 – 10)	5 (2 – 7)	<0.001*

*significant at p<0.05. 1) At baseline, patients are classified as relapse versus no relapse based on the entire follow-up. During follow-up, patients are classified as relapse versus no relapse based on whether they had experienced a relapse prior to (or within 30 days of) answering the questionnaire.

Supplementary Table 2. Time between the baseline endoscopic assessment and anti-TNF discontinuation, with corresponding hazard ratios for partial versus complete endoscopic healing as predictor for the risk of relapse.

	N=	Partial endoscopic healing aHR (95%CI)	P
All patients	81	3.28 (1.43 – 7.50)	0.005*
Colonoscopy <6 months	77	3.44 (1.49 – 7.94)	0.004*
Colonoscopy <3 months	74	3.45 (1.49 – 8.01)	0.004*
Colonoscopy <1.5 month	67	3.45 (1.47 – 8.11)	0.005*
Colonoscopy <3 weeks	56	3.01 (1.10 – 8.25)	0.03*

*Significant at p<0.05

Supplementary Table 3. Predictors of relapse among patients with complete endoscopic healing (n=71), multivariable Cox regression analysis.

	All patients aHR (95%CI)	P	CD patients aHR (95%CI)	P	UC/IBDU patients aHR (95%CI)	P
Subtherapeutic anti-TNF trough level	0.55 (0.23 – 1.28)	0.16	0.63 (0.23 – 2.08)	0.51	0.62 (0.12 – 3.25)	0.57
Immunomodulator use	0.86 (0.38 – 1.93)	0.72	1.40 (0.44 – 4.46)	0.57	0.54 (0.16 – 1.76)	0.30
Mesalamine use	0.13 (0.02 – 1.00)	0.05*	-	-	0.12 (0.01 – 1.05)	0.06

*Significant at p<0.05. aHR: adjusted hazard ratio.

Supplementary Table 4. Post-hoc analysis of other potential predictors of relapse, univariable Cox regression analysis

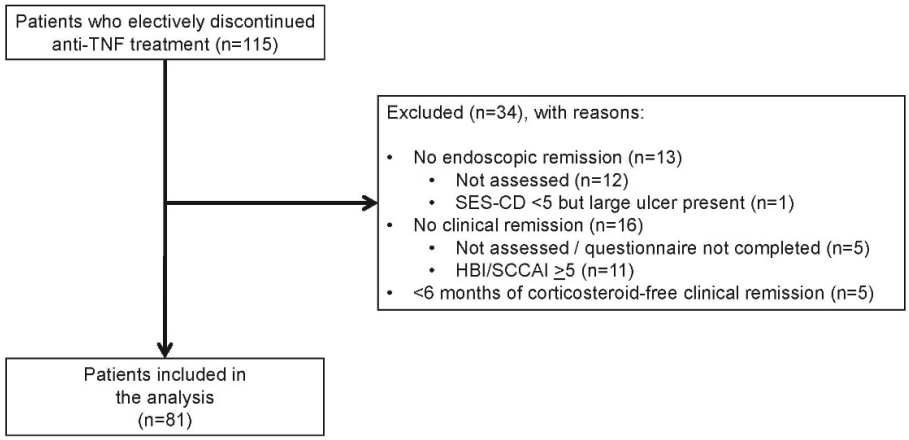
	Univariable	
Variable	**Hazard ratio**	**P-value**
Age at anti-TNF withdrawal (per 10 years)	0.92 (0.75 – 1.14)	0.45
Male sex	0.62 (0.33 – 1.16)	0.14
UC/IBDU (versus CD)	1.10 (0.59 – 2.05)	0.76
Duration of remission (per year)	0.93 (0.82 – 1.06)	0.28
Adalimumab (versus infliximab)	0.98 (0.49 – 1.97)	0.96
CRP (mg/L, per 10-fold increase)	0.67 (0.27 – 1.67)	0.39
Fecal calprotectin (µg/g, per 10-fold increase)	1.16 (0.71 – 1.90)	0.55
White blood cell count (per 1*10^9/L increase)	1.13 (0.97 – 1.31)	0.11
Hemoglobin level (per 1 mmol/L increase)	0.92 (0.63 – 1.34)	0.66
Prior primary non-response/loss of response to anti-TNF	0.81 (0.11 – 5.90)	0.84

Supplementary Table 5. Secondary Outcomes

	All patients (N=81)	**UC/IBDU (n=40)**	**CD (n=41)**
Medication use			
Anti-TNF reintroduction	30 (37.0)	15 (37.5)	15 (36.6)
Other biological/tofacitinib started[1]	7 (8.6)	3 (7.5)	4 (9.8)
Corticosteroid use	19 (23.5)	10 (25.0)	9 (22.0)
Any medication step-up	38 (46.9)	20 (50.0)	18 (43.9)
Alternative definitions of relapse			
Endoscopic relapse	22 (27.2)	9 (22.5)	13 (31.7)
Patient-reported clinical relapse	23 (28.4)	12 (30.0)	11 (26.8)
Fecal calprotectin >250µg/g	34 (42.0)	11 (27.5)	23 (56.1)
CRP >10mg/L	21 (25.9)	6 (7.4)	15 (36.6)
Adverse events / complications			
IBD-related hospitalization	3 (3.7)	1 (2.5)	2 (4.9)
IBD-related surgery	1 (1.2)	0 (0)	1 (2.4)
Perianal abscess/fistula	1 (1.2)	0 (0)	1 (2.4)
Abdominal Abscess/fistula	0 (0)	0 (0)	0 (0)
Intestinal stenosis	2 (2.5)	0 (0)	2 (4.9)

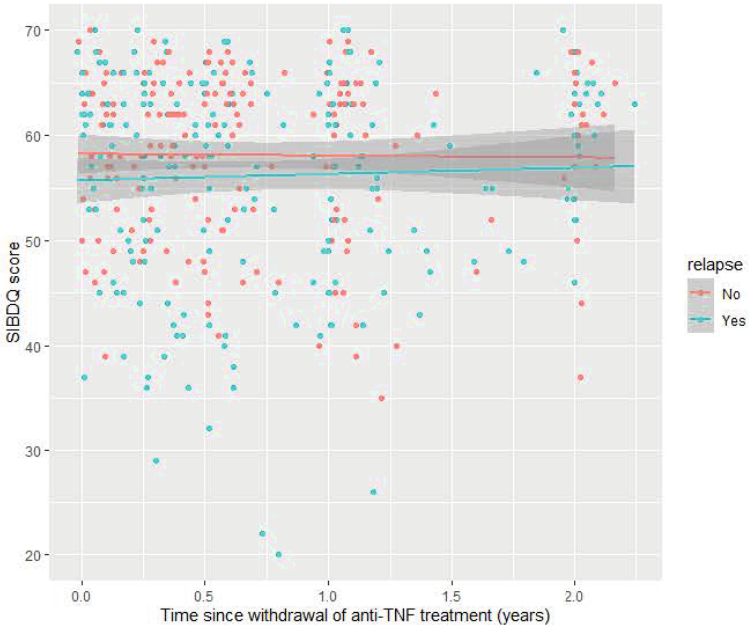
1) 3 patients started vedolizumab immediately after relapse. 4 patients first reinitiated anti-TNF and then switched to vedolizumab (n=1) or ustekinumab (n=3).

Supplementary Figure 1. Flowchart of patient identification



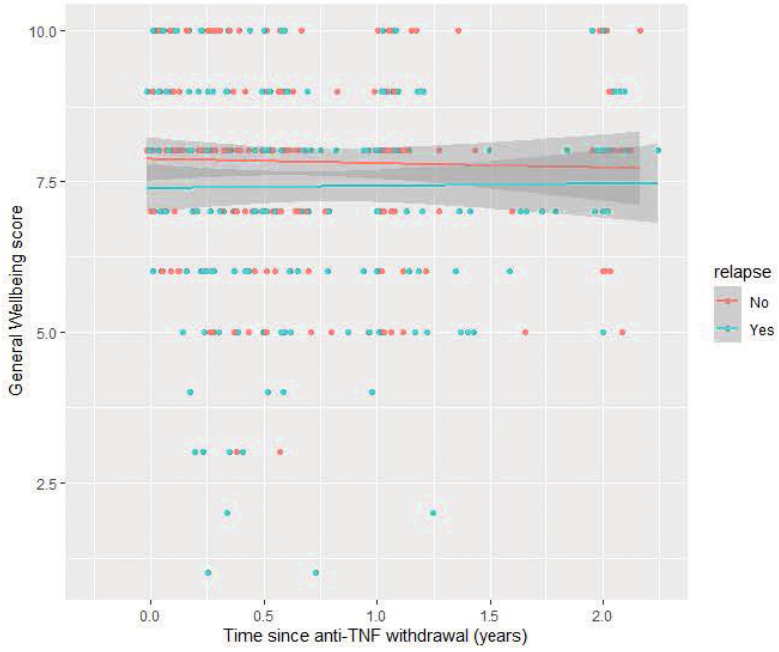
Supplementary Figure 2. Short-IBDQ (A) and general wellbeing scores (B) over time, patients with versus without relapse during follow-up.

A

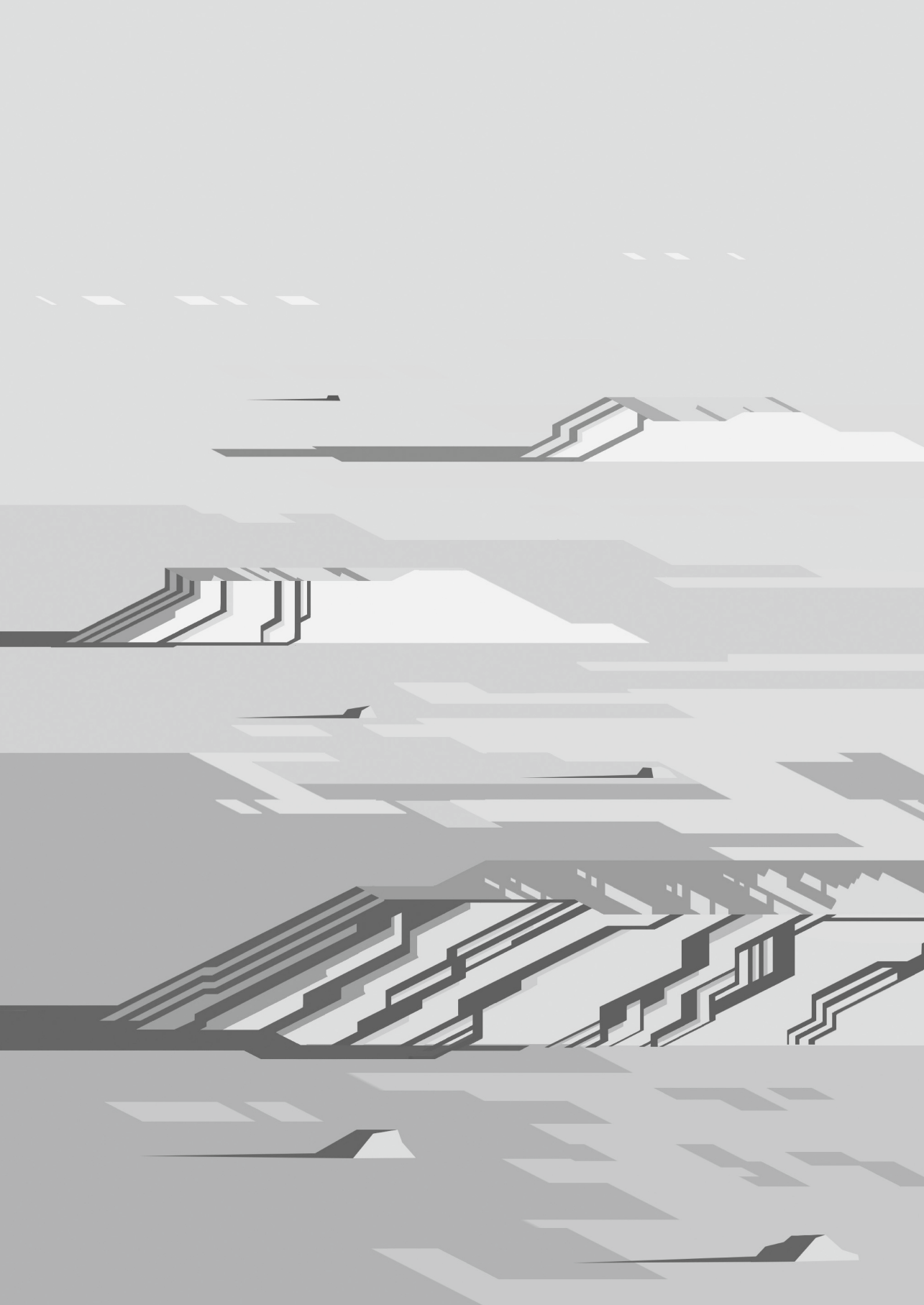


Note: Higher SIBDQ-score indicates higher quality of life.
Effect of time: $-7.9*10^{-4}$, p=0.73; Effect of relapse: -2.8, p=0.13;
Effect of relapse-time interaction: $-1.9*10^{-3}$ p=0.53

B



Note: higher score indicates better wellbeing.
Effect of time: $-1.4*10^{-4}$, p=0.79; Effect of relapse: -0.47, p=0.13;
Effect of relapse-time interaction: $-1.2*10^{-4}$, p=0.87



Chapter 4

Immunomodulator withdrawal from anti-TNF therapy is not associated with loss of response in inflammatory bowel disease

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Clin Gastroenterol Hepatol. 2022 Nov;20(11):2577-2587.

Abstract

Background and aims

The benefit of concomitant immunomodulators (thiopurines or methotrexate) in patients with inflammatory bowel disease (IBD) on anti-TNF (infliximab or adalimumab) maintenance therapy is debated. We compared outcomes after immunomodulator withdrawal versus continuation of combination therapy.

Methods

This was a retrospective cohort study in a general hospital and a tertiary referral center. We included adult IBD patients, receiving anti-TNF for ≥4 months, plus an immunomodulator at baseline, between 01.01.2011-01.01.2019. The primary endpoints were loss of response (LOR, i.e. anti-TNF discontinuation because of disease activity) and anti-drug antibodies. Adjusted hazard rates (aHR) were calculated by mixed-effects Cox regression analysis.

Results

We included 614 treatment episodes of combination therapy in 543 individuals, yielding 1664 patient-years of follow-up. The immunomodulator was withdrawn in 296 (48.2%) episodes after 0.9 (IQR 0.6 – 2.1) years, which was not associated with a higher risk of LOR (aHR 1.08, 95%CI 0.72 – 1.61) although anti-drug antibodies were detected more frequently (aHR 2.14, 95%CI: 1.17 – 3.94), compared with continuation. Clinical remission at the time of withdrawal reduced the risk of LOR (aHR 0.48, 95%CI: 0.25 – 0.93), while longer duration of combination therapy before withdrawal decreased the risk of anti-drug antibodies (HR 0.56 per year, 95%CI: 0.32 – 0.91). Higher pre-withdrawal infliximab trough levels reduced the subsequent risks of anti-drug antibodies and LOR. Infliximab trough levels were lower after immunomodulator withdrawal (p=0.01).

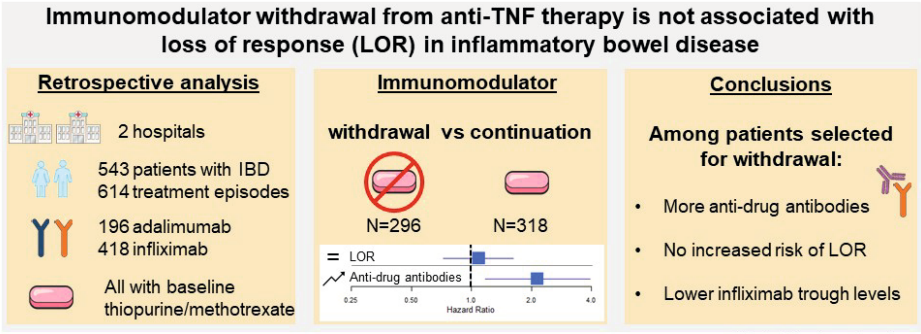
Conclusion

Patients who withdrew the immunomodulator in this retrospective cohort were not at increased risk of LOR within the following 1-2 years, but an increase in anti-drug antibodies was observed. Our findings require prospective validation, preferably in adequately powered randomized-controlled trials.

Keywords

De-escalation, biologicals, remission, azathioprine

Graphical Abstract



Introduction

Combination of the anti-tumor necrosis factor-α (anti-TNF) agent infliximab with immunomodulators (thiopurines or methotrexate) is superior to infliximab monotherapy and is universally recommended in patients with inflammatory bowel diseases (IBD) who start anti-TNF therapy.[1–7] The benefit of combining adalimumab with immunomodulators remains controversial, however.[8,9] American guidelines recommend adalimumab combination therapy, while the European guideline recommends monotherapy for patients with Crohn's disease (CD).[1,2,5]

The increased effectiveness of combining anti-TNF with thiopurines must be carefully balanced against potential side effects, as combination therapy can increase the risks of serious infections and malignancies, including lymphoma.[10,11] In clinical practice, immunomodulators are frequently discontinued during anti-TNF maintenance therapy because of these risks, but the evidence underlying this strategy is limited. Three small randomized-controlled trials found no difference in clinical relapse after immunomodulator discontinuation versus continuation, but these studies were underpowered to detect non-inferiority.[12–14]

We aimed to compare immunomodulator withdrawal versus continuation in a large retrospective cohort of patients with IBD receiving maintenance therapy with infliximab or adalimumab. Next, we aimed to determine whether a longer duration of combination therapy is associated with lower risks of loss of response and anti-drug antibodies after immunomodulator withdrawal.

Methods

Population

In this retrospective cohort study, we identified patients with IBD through the hospital pharmacy and adult gastroenterology department databases of a tertiary referral center (University Medical Center Utrecht) and a large general hospital (St. Antonius Hospital, Nieuwegein) in the Netherlands, using ATC codes for medication and ICD-10 codes for the diagnosis of IBD, as described previously.[15] Inclusion criteria were: a confirmed diagnosis of IBD, at least one year of follow-up at a participating site, at least four months of infliximab or adalimumab treatment started between 01.01.2011–01.01.2019, and combination therapy with an immunomodulator at the start of anti-TNF. We excluded patients with ulcerative colitis (UC) after (sub)total colectomy and patients with an age <18 years at the start of anti-TNF to avoid selection bias (because only adult patients were identified systematically).

If patients were treated repeatedly with anti-TNF during the study period, all episodes meeting the criteria were analyzed. A treatment episode is defined as a continuous timespan

of scheduled anti-TNF treatment. The end of a treatment episode was defined as anti-TNF discontinuation, a switch to another anti-TNF agent, or a drug holiday of more than 90 days. Thus, for example, if a patient was treated with infliximab between 2011-2013 and then with adalimumab from 2015-2016, both episodes were analyzed separately.

Data collection and definitions

Data were collected from the patients' electronic health records, including demographics, disease characteristics, prior medical treatment and relevant comorbidity.

Combination therapy was defined as continuing an immunomodulator (methotrexate, azathioprine, 6-mercaptopurine or thioguanine) after starting anti-TNF treatment, or starting an immunomodulator within 30 days. European guidelines were followed for dosing of immunomodulators.[16] Any (interruption in) immunomodulator use of less than 30 days was ignored. Immunomodulator withdrawal was defined as discontinuation of the immunomodulator, while continuing the anti-TNF for at least 30 days. At the time of immunomodulator withdrawal, we noted whether patients were in corticosteroid-free clinical remission, based on the assessment of the treating physician.

Reasons for discontinuing anti-TNF or immunomodulators were classified as loss of response (anti-TNF only), therapeutic de-escalation, side effects, patient's initiative or "other". Loss of response was defined as anti-TNF discontinuation because of disease activity (as documented by the treating physician, usually based on symptoms with at least one adjunctive endoscopic, radiographic or biochemical finding). De-escalation was defined as elective drug discontinuation, in order to reduce the risk of future drug-related adverse events, to meet patient preference and/or to provide cost savings.[17]

Anti-TNF dose (de-)escalations were recorded, defined as any change in dosage or dosing interval from standard regimens (5mg/kg per 8 weeks for infliximab and 40mg/2 weeks for adalimumab). C-reactive protein (CRP) and fecal calprotectin were recorded at the start of anti-TNF, at immunomodulator withdrawal (maximum of 4 months before or 2 months after) and at anti-TNF discontinuation. All measurements of anti-TNF trough levels and anti-drug antibodies were extracted. Reactive therapeutic drug monitoring was the standard of care during the study period.

Outcomes

The primary outcomes were loss of response and detection of anti-drug antibodies to anti-TNF. Secondary outcomes were anti-TNF dose escalations, anti-TNF discontinuation and anti-TNF trough levels.

Statistical analysis

Continuous parameters were described as medians with interquartile ranges (IQR) with Mann-Whitney U test for significance. For categorical parameters, Chi-square or Fisher's exact tests were performed.

Immunomodulator withdrawal versus continuation was analyzed with mixed-effects Cox regression analysis, regardless of subsequent immunomodulator reintroduction (i.e. *intention-to-treat*). Time at risk started at the maintenance phase (four months after anti-TNF initiation). Immunomodulator withdrawal was analyzed as a time-varying covariate to prevent *immortal time bias*, meaning that all patients initially contributed follow-up time to the "continuation" group, and then switched to the "withdrawal" group, if applicable, with a delay of 90 days.[18] Of note, this time-varying analysis precluded construction of Kaplan-Meier curves comparing immunomodulator withdrawal versus continuation. Patients were censored at anti-TNF discontinuation, 01.12.2019 or last available follow-up.

Multiple imputations were performed to replace missing values, and the regression model was adjusted for multiple treatment episodes in individual patients (**Supplementary methods**), and potential confounders: age, sex, IBD phenotype, smoking, BMI, primary sclerosing cholangitis, rheumatologic comorbidity, infliximab versus adalimumab, prior anti-TNF exposure and disease duration. We performed subgroup analyses for patients with UC, patients with CD, infliximab-treated and adalimumab-treated patients, and anti-TNF naïve patients (i.e. no prior exposure to anti-TNF or other biological). Per definition, in the subgroup analysis of anti-TNF naïve patients, only one treatment episode was analyzed per patient. Sensitivity analyses (**Supplementary Table 1**) were performed for the primary outcomes in patients with prior biological exposure, patients with at least 4 months of combination therapy, and for thiopurine withdrawal (excluding methotrexate), and significant differences from the primary analyses are reported in the main text.

Among those who stopped the immunomodulator, predictors of loss of response and immunogenicity were identified using Cox regression analysis. Time at risk started at the time of immunomodulator withdrawal. Parameters with $p<0.20$ on univariable analysis were entered in the multivariable model. Anti-TNF trough levels, CRP and fecal calprotectin were only evaluated on univariable analysis, due to limited data availability. Kaplan Meier curves are presented with log-rank tests for significance.

Longitudinal analysis of infliximab and adalimumab trough levels was performed employing mixed-effects linear regression analysis, adjusted for dose (de)escalations, anti-drug antibodies and repeated measurements in individual patients, among others (**Supplementary methods)**.

All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value of <0.05 was considered significant.

Study oversight

This study received exempt status from the institutional review board of the University Medical Center Utrecht, because of its observational design.

Results

Cohort Characteristics

Among 614 episodes of combination therapy in 543 individual patients (**Supplementary Figure 1)**, the immunomodulator was discontinued in 296 (48.2%) episodes, after a median of 0.9 (IQR 0.6-2.1) years. Patients who discontinued the immunomodulator had a higher BMI, were more often anti-TNF naïve and had longer follow-up (until anti-TNF discontinuation or censoring) than those who continued the immunomodulator **(Table 1)**. At the time of immunomodulator withdrawal, 85% of patients were in clinical remission. The immunomodulator was most frequently discontinued as a de-escalation strategy (**Figure 1).** The median follow-up after immunomodulator withdrawal was 1.7 (IQR 0.8-3.5) years.

Table 1. Baseline Characteristics

	IMM continuation (n=318)	IMM withdrawal (N=296)	p-value
Female sex	173 (54.4)	168 (56.8)	0.56
IBD type			0.37
Crohn's disease	224 (70.4)	208 (70.3)	
Ulcerative colitis	88 (27.7)	77 (26.0)	
IBD-unclassified	6 (1.9)	11 (3.7)	
BMI	24.6 (21.5 – 27.5)	25.2 (22.4 – 29.2)	**0.02***
Active Smokers	77 (25.1)	67 (23.8)	0.71
Concomitant PSC	13 (4.1)	7 (2.4)	0.23
Rheumatologic comorbidity	42 (13.2)	41 (13.9)	0.82
Age at IBD diagnosis (years)	24.5 (19.6 – 36.0)	25.6 (21.0 – 38.3)	0.18
Crohn's Disease behavior			0.47
Inflammatory (B1)	99 (44.2)	86 (41.3)	
Stricturing (B2)	79 (35.3)	85 (40.9)	
Penetrating (B3)	46 (20.5)	37 (17.8)	
Crohn's Disease location			0.51
Ileal (L1)	61 (27.2)	63 (30.3)	
Colonic (L2)	47 (21.0)	32 (15.4)	0.99
Ileocolonic (L3)	114 (50.9)	111 (53.4)	
Isolated upper GI (L4)	2 (0.9)	2 (0.1)	
L1/L2/L3 + upper GI (L4)	27 (12.2)	24 (11.7)	
Perianal Crohn's disease	75 (33.5)	72 (34.6)	0.80

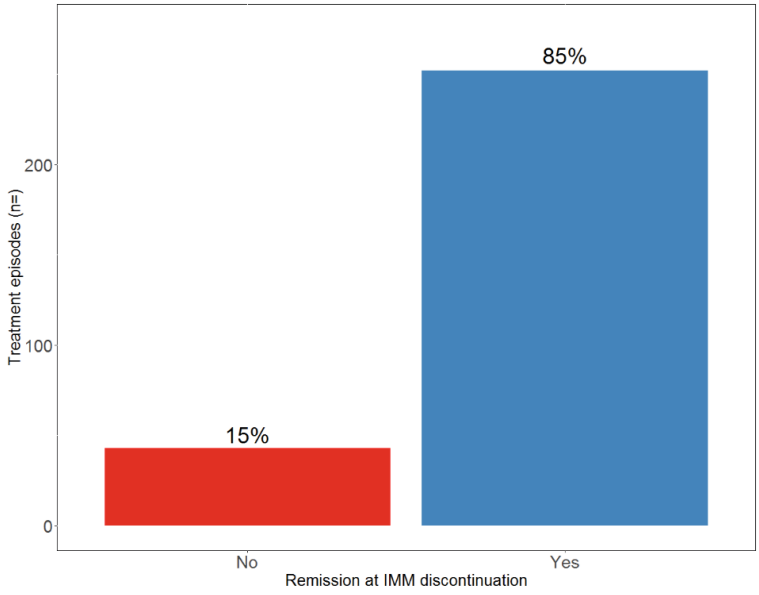
Table 1. Baseline Characteristics (continued)

	IMM continuation (n=318)	IMM withdrawal (N=296)	p-value
UC/IBDU Disease extent			0.19
Proctitis (E1)	3 (3.2)	6 (6.8)	
Left-sided (E2)	35 (37.2)	23 (26.1)	
Extensive (E3)	56 (59.6)	59 (67.0)	
Prior IBD-related surgery[1]	59 (18.6)	64 (21.6)	0.34
Treatment characteristics			
Adalimumab (vs infliximab)	107 (33.6)	89 (30.1)	0.34
Duration of follow-up (years)	1.7 (0.9 – 3.1)	3.6 (2.0 – 5.4)	**<0.001***
Disease duration at start (years)	4.1 (1.2 – 11.8)	4.1 (1.3 – 11.0)	0.69
Age at start (years)	32.7 (24.9 – 49.9)	34.7 (25.8 – 50.0)	0.40
Prior biological-exposure			
None (*anti-TNF naïve*)	208 (65.4)	223 (75.3)	**0.01***
Prior anti-TNF	110 (34.6)	73 (24.7)	**0.01***
Prior anti-TNF and vedolizumab/ ustekinumab	8 (3.7)	0	**0.004***
Prior medication exposure			
Systemic steroids	258 (86.6)	240 (85.4)	0.69
Thiopurines	277 (87.9)	267 (90.2)	0.37
Methotrexate	37 (11.7)	38 (12.9)	0.67
Prior IMM failure[2]	137 (66.5)	150 (67.3)	0.87
Current immunomodulator			0.22
Thiopurine	290 (92.1)	264 (89.2)	
Methotrexate	25 (7.9)	32 (10.8)	
Duration of combination therapy prior to IMM withdrawal (years)	-	0.9 (0.6 – 2.1)	-
CRP at IMM withdrawal (mg/L)		2.0 (0.0 – 4.0)	-
FCP at IMM withdrawal (ucg/g)		62 (24.0 – 194.0)	-
Infliximab trough level at IMM withdrawal (mg/L)		5.3 (4.0 – 9.0)	-
Adalimumab trough level at IMM withdrawal (mg/L)		9.3 (6.7 – 11.3)	-

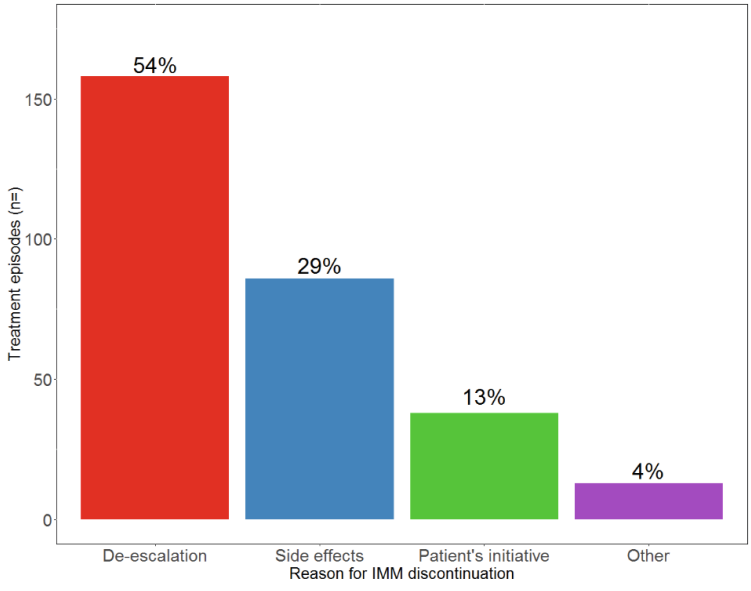
IMM: immunomodulator. Missing: BMI (n=26), smoking (n=25), upper GI involvement (n=4), Prior medication (thiopurines [n=3], steroids [n=35], methotrexate [n=4]), CRP (n=49), FCP (n=175), trough levels (infliximab [n=99], adalimumab [n=53]). *Significant at p<0.05. 1) Bowel resection, stricturoplasty of fecal diversion. 2) subgroup of anti-TNF naïve patients.

Figure 1. Frequencies of clinical remission at the time of immunomodulator withdrawal (A) and reasons for immunomodulator withdrawal (B).

A



B



Loss of response and immunogenicity

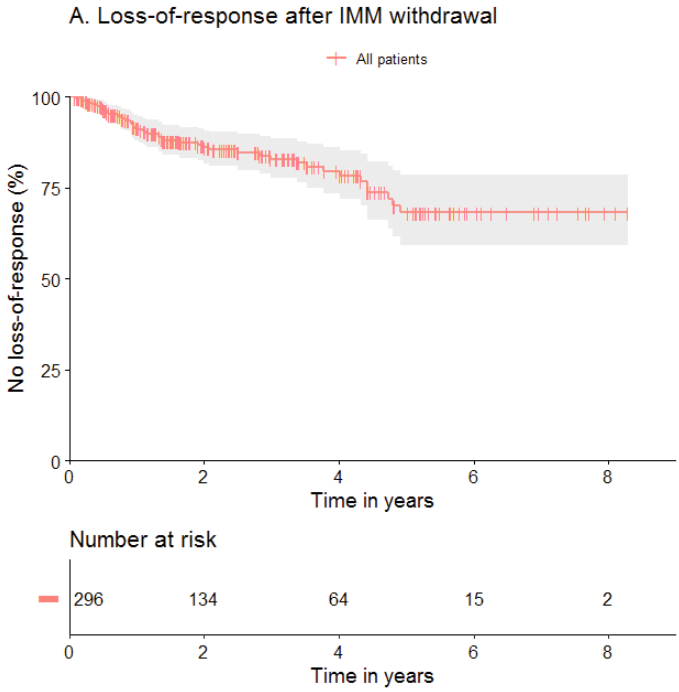
After immunomodulator discontinuation, loss of response to anti-TNF occurred in 46 (15.5%) patients, at a rate of 6.6% per patient-year (95%CI: 4.8-8.8). The estimated duration at which 25% of the cohort experienced loss of response was 4.4 years (95%CI: 3.8-upper limit not reached, **Figure 2A**). At the time of loss of response, the median fecal calprotectin and CRP levels were 1004µcg/g (IQR: 254-2034) and 6.8mg/L (IQR 2.0-18.0), respectively.

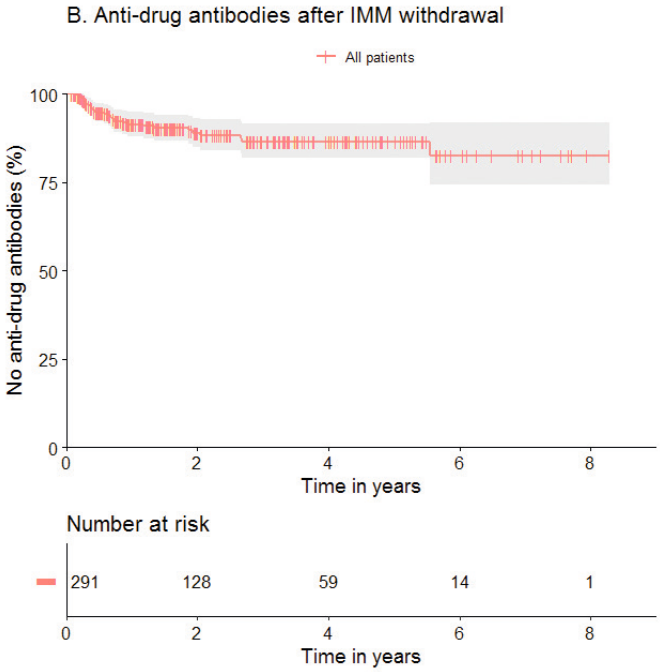
Immunomodulator withdrawal did not increase the risk of loss of response in the total cohort (aHR 1.08, 95%CI 0.72-1.61), or in the subgroup analyses (**Figure 3A**), compared with immunomodulator continuation. Relative to CD, more UC patients experienced loss of response during combination therapy (n=37, 39.4%), resulting in a lower risk estimate for immunomodulator withdrawal versus continuation (aHR 0.68, 95%CI 0.29-1.55), albeit with a wide confidence interval due to the smaller sample size (**Figure 3A**).

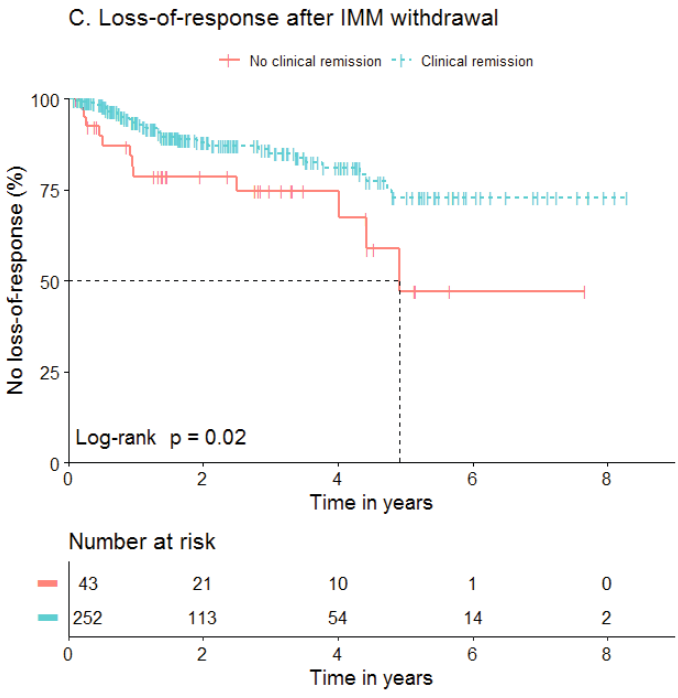
Anti-drug antibodies were detected in 30 (10.3%) patients following immunomodulator withdrawal, at a rate of 4.5% per patient-year (95%CI: 3.1-6.5, **Figure 2B**). The incidence of anti-drug antibody detection was higher within versus after 12 months following withdrawal (9.1% per patient-year; 95%CI: 5.7-13.7 versus 1.9%;95%CI: 0.8-3.8). Immunomodulator discontinuation was associated with an increased risk of anti-drug antibodies in the entire cohort (aHR 2.14, 95%CI: 1.17-3.94), which did not reach statistical significance in the subgroups of patients with adalimumab, CD patients, UC patients (**Figure 3B**) and biological-exposed patients (**Supplementary Table 1**).

After detection of anti-drug antibodies, 37 (57.8%) patients developed loss of response, of whom 75% discontinued anti-TNF within 3 months. In patients with anti-drug antibodies, the risk of loss of response (data not shown, p=0.31) and the antibody titers were similar between those who had continued or withdrawn the immunomodulator (median: 48 AU/mL, IQR: 16-270 versus 79 AU/mL, IQR: 29-125, p=0.70).

Figure 2. Kaplan Meier estimates. A) Loss of response following immunomodulator withdrawal, all patients. B) Anti-drug antibodies following immunomodulator withdrawal, all patients. C) Loss of response following immunomodulator withdrawal, stratified by clinical remission status at timing of immunomodulator withdrawal. D) Anti-drug antibodies following immunomodulator withdrawal, stratified by duration of combination therapy prior to stopping the immunomodulator.




B. Anti-drug antibodies after IMM withdrawal
All patients
No anti-drug antibodies (%)
100
75
50
25
0
0
2
4
6
8
Time in years
Number at risk
291
128
59
14
1
0
2
4
6
8
Time in years


C. Loss-of-response after IMM withdrawal
No clinical remission
Clinical remission
No loss-of-response (%)
100
75
50
25
0
Log-rank p = 0.02
0
2
4
6
8
Time in years
Number at risk
43
21
10
1
0
252
113
54
14
2
0
2
4
6
8
Time in years

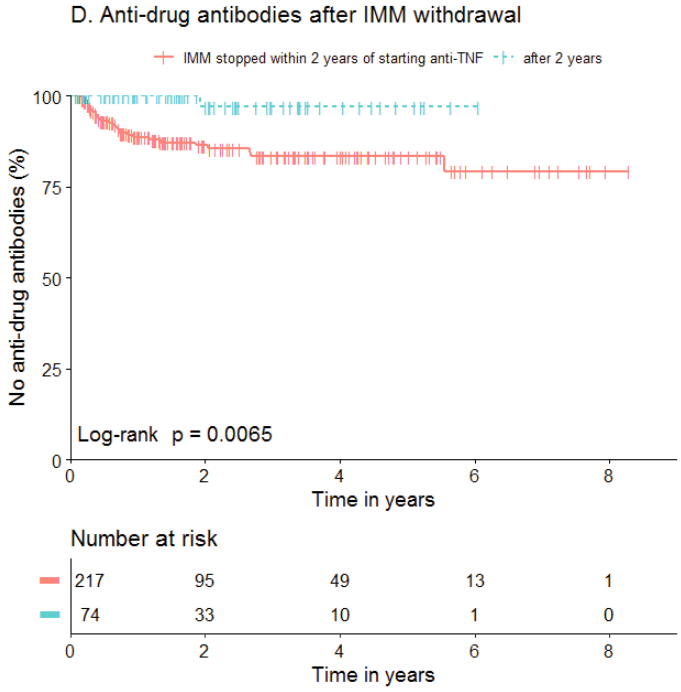
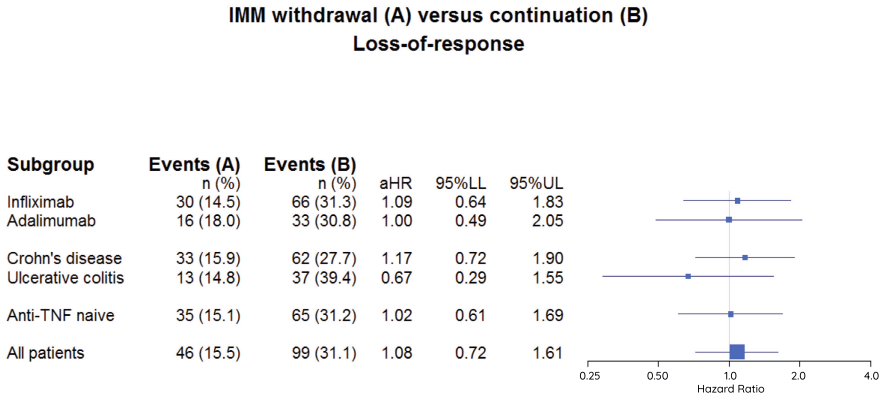
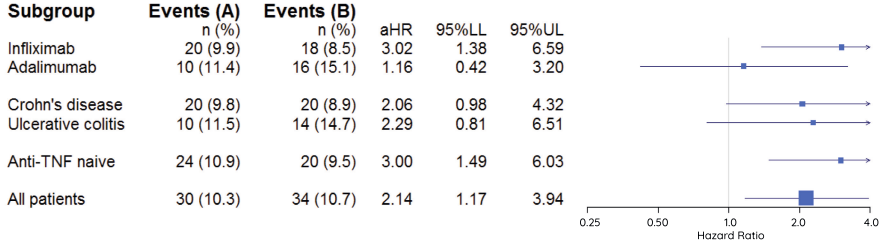

D. Anti-drug antibodies after IMM withdrawal
IMM stopped within 2 years of starting anti-TNF
after 2 years
No anti-drug antibodies (%)
100
75
50
25
0
Log-rank p = 0.0065
0
2
4
6
8
Time in years
Number at risk
217
95
49
13
1
74
33
10
1
0
0
2
4
6
8
Time in years

Figure 3. Multivariable hazard ratios of immunomodulator withdrawal versus continuation for A) loss of response and B) anti-drug antibodies. 95%LL/UL: lower limit/upper limit of 95% confidence interval.

A



B



Predictors of successful immunomodulator withdrawal

Among patients who discontinued the immunomodulator, clinical remission at the time of immunomodulator withdrawal was independently associated with a lower rate of loss of response (aHR 0.48, 95%CI: 0.25-0.93) **(Table 2, Figure 1C**). A higher CRP (HR 1.31, 95%CI: 1.09-1.58, natural-log transformed) or fecal calprotectin (HR 1.34, 95%CI: 1.06-1.70, natural-log transformed) at immunomodulator withdrawal were associated with loss of response (if available). Routinely used thresholds for disease activity, i.e. CRP >10mg/L (n=25, 10.1%) and fecal calprotectin >250µcg/g (n=24, 19.8%), resulted in

numerically higher risk estimates for loss of response, but this did not reach statistical significance (HR for CRP: 2.00, 95%CI 0.80-4.98; HR for fecal calprotectin: 2.36, 95%CI 0.85-6.50).

Higher pre-withdrawal infliximab trough levels (HR: 0.43, 95%CI: 0.24-0.77, natural-log transformed, available in 108 [52.2%]) were found to reduce the risk of loss of response (**Table 2**), and a similar trend was observed for adalimumab (HR 0.12, 95%CI 0.01-1.03). Details regarding the last trough level measurement prior to immunomodulator withdrawal are presented in **Supplementary Table 2**.

A longer duration of combination therapy prior to immunomodulator withdrawal was associated with a 46% reduced rate of anti-drug antibody detection after immunomodulator discontinuation (HR 0.54, 95%CI 0.32-0.91, **Table 2**). Moreover, a 72% reduction in the detection rate of anti-drug antibodies (HR 0.28, 95%CI: 0.13-0.60) was observed for higher infliximab trough levels prior to immunomodulator withdrawal, per point on the natural log scale (e.g. between infliximab levels of 12.2mg/L versus 4.5mg/L, or 4.5mg/L versus 1.6mg/L). No multivariable analysis was conducted for anti-drug antibodies as only one variable was identified with p<0.20 on univariable analysis and limited trough level measurements.

Distinct intervals (<0.5, 0.5-1, 1-2 and >2 years) of combination therapy were analyzed, but no difference in the risk of loss of response was observed (**Supplementary figure 2a,** p=0.39). In contrast, more than 2 years of combination therapy was associated with a lower risk of anti-drug antibodies (**Supplementary Figure 2b, Figure 1D,** p=0.007). Reasons for immunomodulator withdrawal were not associated with loss of response (p=0.41) or anti-drug antibodies (p=0.11, **Supplementary Figure 2C and D**).

Table 2. Predictors of loss of response and anti-drug antibodies after immunomodulator withdrawal (n=296)

	Loss of response (46 events)				**Anti-drug antibodies (30 events)**	
	Univariable		**Multivariable**		**Univariable**	
	HR (95%CI)	p-value	aHR (95%CI)	p-value	HR (95%CI)	p-value
Smoking	0.44 (0.19 – 1.05)	0.06	0.47 (0.20 – 1.12)	0.08	1.13 (0.48 – 2.66)	0.78
UC (versus CD)	1.01 (0.53 – 1.93)	0.96	-	-	1.29 (0.58 – 2.87)	0.53
Male sex	0.96 (0.54 – 1.73)	0.90	-	-	0.83 (0.39 – 1.79)	0.64
BMI	1.01 (0.96 – 1.07)	0.61	-	-	1.04 (0.97 – 1.11)	0.24
ADA (versus IFX)	1.05 (0.57 – 1.94)	0.87	-	-	1.11 (0.50 – 2.46)	0.79
No prior anti-TNF exposure	1.06 (0.54 – 2.09)	0.87	-	-	1.34 (0.53 – 3.39)	0.53
Duration of combination therapy	0.85 (0.64 – 1.11)	0.23	-	-	0.54 (0.32 – 0.91)	**0.02***
Clinical remission at IMM withdrawal	0.47 (0.24 – 0.90)	**0.02***	0.48 (0.25 – 0.93)	**0.03***	0.63 (0.24 – 1.62)	0.34
CRP at IMM withdrawal[1]	1.31 (1.09 – 1.58)	**0.005***	-	-	1.14 (0.93 – 1.42)	0.20
Fecal calprotectin at IMM withdrawal[1]	1.34 (1.06 – 1.70)	**0.01***	-	-	1.01 (0.82 – 1.25)	0.90
Adalimumab trough level[1]	0.12 (0.01 – 1.03)	0.054	-	-	3.97 (0.06 – 250.5)	0.51
Infliximab trough level[1]	0.43 (0.24 - 0.77)	**0.004***	-	-	0.28 (0.13 – 0.60)	**0.001***

*Significant at p<0.05. 1) CRP (mg/L), fecal calprotectin (ucg/g), adalimumab and infliximab trough levels (mg/L) are natural log-transformed, and not entered in the multivariable model due to missing data.

Dose escalations and anti-TNF discontinuation

Dose escalations were required at a rate of 18.0% per patient-year (95%CI: 14.1-22.6) after immunomodulator withdrawal, which was higher compared with immunomodulator continuation (aHR 1.36, 95%CI 0.97-1.89). This did not reach statistical significance in the entire cohort, nor in the subgroup analyses, however (**Supplementary Table 3).** No differences were observed in the rate of anti-TNF discontinuation between those who stopped versus continued the immunomodulator (aHR 0.95, 95%CI 0.71-1.26, **Supplementary table 4**).

Evolution of anti-TNF trough levels

Infliximab trough levels decreased significantly after immunomodulator withdrawal (**Supplementary figure 3A,** p=0.01). Mean unadjusted trough levels of infliximab were 6.3mg/L (standard deviation [SD] 5.6, 669 measurements) during combination therapy, versus 5.7mg/L (SD: 4.5, 533 measurements) after withdrawal of the immunomodulator. Adalimumab trough levels did not decrease after immunomodulator withdrawal (**Supplementary figure 3B,** p=0.16).

Immunomodulator reintroduction

The immunomodulator was reintroduced in 47 (16.2%) patients after a median of 0.6 (IQR 0.4-1.6) years following withdrawal, which did not prevent subsequent loss of response in 15 (31.9%) patients. Seven (14.9%) patients reintroduced the immunomodulator after detection of anti-drug antibodies, which resulted in detectable anti-TNF trough levels in all seven patients (range: 1.5-19.2), but anti-drug antibodies persisted or recurred in two patients (28.6%).

Discussion

In this large retrospective cohort study, we comprehensively analyzed immunomodulator withdrawal versus continuation in patients with IBD treated with anti-TNF combination therapy. Although a quarter of patients experienced loss of response at 4.4 years after stopping the immunomodulator, this was not significantly different from patients in whom the immunomodulator was continued. Immunomodulator withdrawal was associated with increased detection of anti-drug antibodies, and lower infliximab trough levels. A longer duration of combination therapy before immunomodulator withdrawal was associated with a subsequent lower rate of anti-drug antibody detection.

Given the safety profile of anti-TNF combination therapy with well-documented higher risks of malignant lymphoma and serious infections,[11,19] there is an urgent clinical need to define strategies for therapeutic de-escalation in patients with IBD in remission.[17] Withdrawal of immunomodulators in patients receiving combination therapy is currently recommended by the European guideline in patients with CD achieving long-term remission[5], while other guidelines provide no recommendation.[1–4] Three small randomized-controlled studies

compared immunomodulator withdrawal versus continuation in patients with CD, and detected no difference in clinical relapse or anti-TNF discontinuation, although in one study CRP increased and infliximab trough levels decreased (as in our study).[12–14] Unfortunately, these studies were underpowered with limited follow-up. In line with previous studies, we report no increased risk of loss of response or anti-TNF discontinuation after immunomodulator withdrawal. However, we did find a significant increase in the detection rate of anti-drug antibodies after immunomodulator discontinuation, especially in patients treated with infliximab. The discrepancy between the increase in anti-drug antibodies and lower trough levels after stopping the immunomodulator, but no corresponding higher risk of loss of response after immunomodulator withdrawal, is striking. It has been reported that anti-drug antibodies can be overcome by dose escalation or immunomodulator (re) initiation.[20–22] This is line with the observed higher frequency of dose escalations after immunomodulator withdrawal, although this finding did not reach statistical significance.

Patients who received combination therapy for a longer time, were at lower risk of anti-drug antibodies after immunomodulator withdrawal, but longer duration of combination therapy did not prevent loss of response. In contrast to our findings, several prior studies did report a significantly lower risk of loss of response with longer combination therapy (with optimal cut-offs at 6 months, 9 months or 2.2 years)[23–25], but not all.[26,27] Notably, a protective effect of longer duration of combination therapy might also be attributed to selection of low-risk patients over time, rather than a direct protective effect of the continued immunomodulator. Thus, the optimal duration of combination therapy remains to be determined. Other risk factors for relapse after immunomodulator discontinuation were identified in prior retrospective studies, including low infliximab trough levels (<5µcg/mL), high CRP (>5mg/L), high platelet count[23], prior infliximab dose-escalation[27], discontinuation of methotrexate (instead of thiopurine)[25] and young age at diagnosis (<16y).[25] In our study, we additionally found that absence of clinical remission and higher fecal calprotectin were risk factors for loss of response after immunomodulator discontinuation, and confirmed that higher anti-TNF trough levels are protective.

General strengths of our study include the systematic identification of patients, large sample size, relatively long duration of follow-up and detailed data collection, allowing a comprehensive analysis of both clinical, biochemical and pharmacokinetic outcomes following immunomodulator withdrawal. We addressed knowledge gaps in prior literature by providing subgroup analyses for patients with UC[24] and adalimumab-treated patients.[13] In contrast to infliximab, the occurrence of anti-adalimumab antibodies was not increased after stopping the immunomodulator. Inclusion of patients using methotrexate (versus thiopurine) enhanced generalizability of our findings. While our primary findings remained unchanged in the sensitivity analysis excluding methotrexate, our study was not designed to detect differences between methotrexate versus thiopurine combination therapy.

The limitations inherent to the retrospective design of our study should also be acknowledged. Despite our careful employment of statistical techniques to balance patients' characteristics, there is a plausible, unmeasurable bias towards selection of low-risk patients for immunomodulator withdrawal from combination therapy that can only be overcome in randomized-controlled studies. Furthermore, transient (symptomatic) flares that did not result in anti-TNF dose escalation or loss of response were not detected with our study design. Prospective studies may provide more details regarding clinical symptoms, endoscopic outcomes, dosing of immunomodulators, as well as scheduled measurements of CRP, fecal calprotectin, trough levels and anti-drug antibodies. Nevertheless, these limitations must be contrasted with higher generalizability of our study providing real-world data, longer follow-up, and the large sample size that allowed assessment of predictors of successful immunomodulator withdrawal.

Expanding treatment options for IBD in case of failure of anti-TNF, including biologicals with other molecular targets and small molecules,[28] shed a new light on the risks versus benefits of prolonged combination therapy of anti-TNF with thiopurines. With new treatment options, the theoretically increased risk of anti-TNF failure after immunomodulator discontinuation may no longer outweigh the long-term side effects of thiopurines. In general, patients receiving combination therapy are willing to de-escalate medical therapy when remission is achieved, and prefer to stop the immunomodulator rather than the anti-TNF agent.[29]

In conclusion, in this retrospective analysis, immunomodulator withdrawal did not result in an increased risk of loss of response to anti-TNF in the following 1-2 years post-cessation, although we observed an increase in anti-drug antibodies and lower infliximab trough levels. Therapeutic drug monitoring and objectifying (biochemical) remission prior to immunomodulator withdrawal may further reduce the risk of loss of response. As the majority of patients were selected by their treating physicians for treatment de-escalation, our findings require prospective validation, preferably in an adequately powered randomized-controlled trial.

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Supplementary Methods

Cox Regression analysis

Adjusted hazard ratios (aHR) were calculated utilizing mixed-effects Cox regression analysis, accounting for multiple treatment episodes in individual patients. The proportional hazards assumption was assessed using Schoenfeld residuals. Disease duration violated the assumption and was entered as a stratum instead of covariate in the model. Multiple imputations were performed to replace missing values for BMI and smoking. CRP, fecal calprotectin and infliximab trough levels were not imputed due to the larger amount of missing data. We assumed that the data were missing at random and performed multiple imputations based on iterative (20 iterations) chained equations with BMI, smoking, length, weight, sex, age, IBD phenotype, hazard of loss of response (Nelson-Aalen estimate), mucosal healing, dose escalations, adalimumab versus infliximab, number of prior anti-TNF exposures, disease duration, Crohn's disease behavior and upper gastrointestinal involvement. Thus, we created 10 imputed datasets using the MICE package in R.13.

Longitudinal analysis of trough levels

Trough levels were analyzed employing a mixed-effects linear regression model of log-transformed trough levels. We used a mixed-effects model, clustering measurements per individual patient. Stopping the immunomodulator was entered as a time-varying covariate. Relevant confounders and potential interactions between confounders were selected using forward and backward selection of models using the Akaike information criterion. The most optimal model for adalimumab was corrected for dose escalations, dose de-escalations, anti-drug antibodies, BMI and prior anti-TNF exposure. The model for infliximab was adjusted for dose escalations, dose de-escalations, anti-drug antibodies, whether the measurement was performed during infliximab induction and a statistical interaction between dose de-escalations and presence of anti-drug antibodies. A thousand bootstraps of the model were performed to obtain both bias-reduced longitudinal profiles of trough levels and predictors.

Supplementary Table 1. Sensitivity analyses. Multivariable hazard ratios for loss of response and anti-drug antibodies. Immunomodulator withdrawal versus continuation.

	Events IMM withdrawal n (%)	Events IMM continuation n (%)	aHR	95%CI Lower limit	95%CI Upper limit
Loss of response					
Patients with >4 months of combination therapy	41 (15.5)	99 (31.1)	1.07	0.71	1.61
Patients with prior biological exposure	11 (15.1)	34 (30.9)	1.09	0.51	2.35
Patients with a thiopurine (and not methotrexate) as immunomodulator	41 (15.5)	91 (31.4)	1.02	0.66	1.58
Anti-drug antibodies					
Patients with >4 months of combination therapy	25 (9.7)	34 (10.7)	2.18	1.18	4.05
Patients with prior biological exposure	6 (8.5)	14 (12.8)	0.83	0.25	2.81
Patients with a thiopurine (and not methotrexate) as immunomodulator	28 (9.6)	26 (10.0)	1.96	1.02	3.77

Supplementary Table 2. Details of last anti-TNF trough level measurement prior to immunomodulator withdrawal, with univariable hazard ratios for loss of response and anti-drug antibodies

	Available in n(%)	Time from last measurement to IMM stop (days)	median trough level mg/L (IQR)	Loss of response n= (%)	HR Loss of response (95%CI)	p	antibodies n= (%)	HR antibodies (95%CI)	p
Adalimumab	36 (40.4)	100 (27 – 323)	9.3 (6.7 – 11.3)	8 (22.2)	0.74 (0.55-1.00)	0.05	1 (2.9)	1.09 (0.74 - 1.59)	0.66
log-transformed	-	-	-	-	0.12 (0.01 - 1.03)	0.054	-	3.97 (0.06 - 250.5)	0.51
Infliximab	108 (52.2)	73 (25 – 196)	5.3 (4.0 – 9.0)	12 (11.1)	0.85 (0.69 - 1.05)	0.13	6 (5.8)	0.74 (0.56 - 0.99)	**0.04***
log-transformed	-	-	-	-	0.43 (0.24 - 0.77)	**0.004***	-	0.28 (0.13 - 0.60)	**0.001***

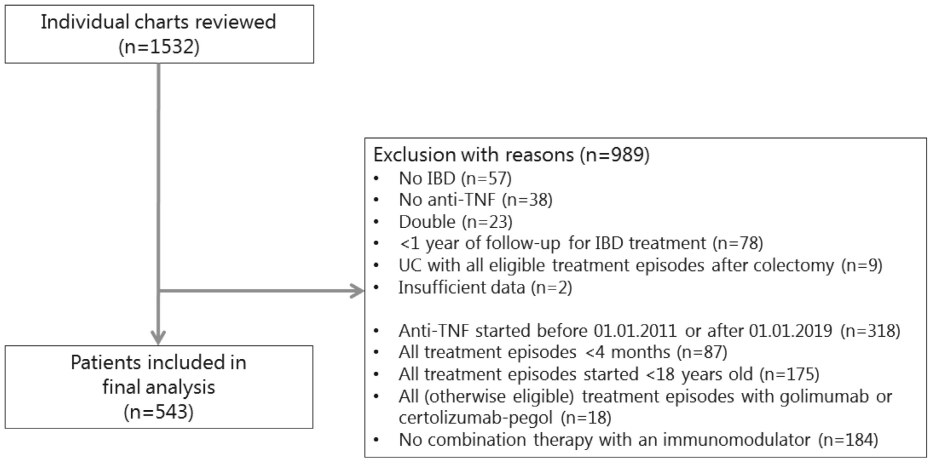
Supplementary Table 3. Multivariable hazard ratios for dose escalation. Immunomodulator withdrawal versus continuation.

(sub)group	Events IMM withdrawal n (%)	Events IMM continuationn (%)	aHR	95%CI Lower limit	95%CI Upper limit
IFX	51 (32.1)	109 (49.1)	1.35	0.91	2.00
ADA	23 (29.5)	42 (42.4)	1.34	0.72	2.49
CD	54 (32.3)	107 (46.5)	1.34	0.92	1.96
UC	20 (28.6)	44 (48.4)	1.21	0.62	2.33
Anti-TNF naïve	58 (32.6)	101 (45.7)	1.43	1.00	2.07
ALL Patients	74 (31.2)	151 (47.0)	1.36	0.97	1.89

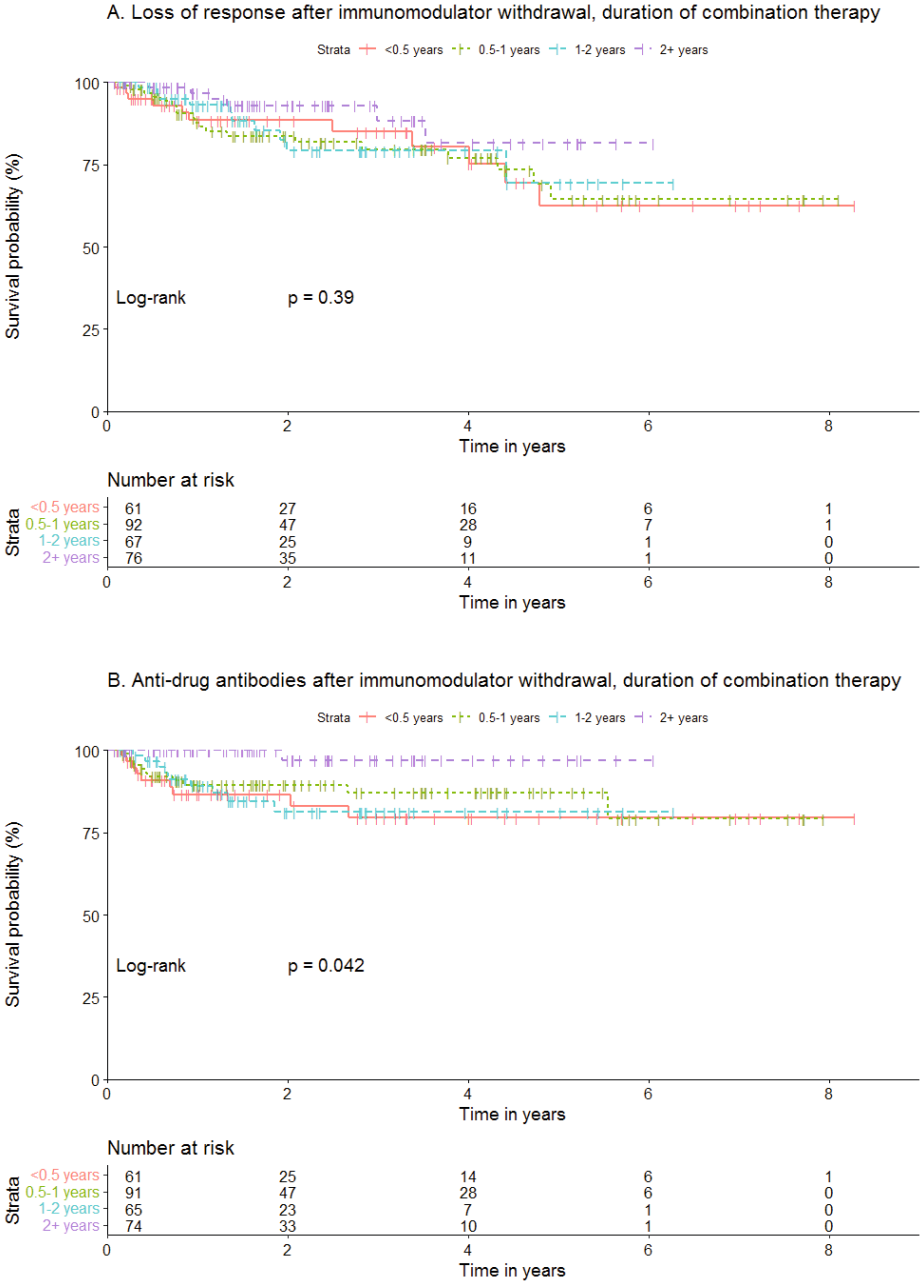
Supplementary Table 4. Multivariable hazard ratios for anti-TNF discontinuation. Immunomodulator withdrawal versus continuation.

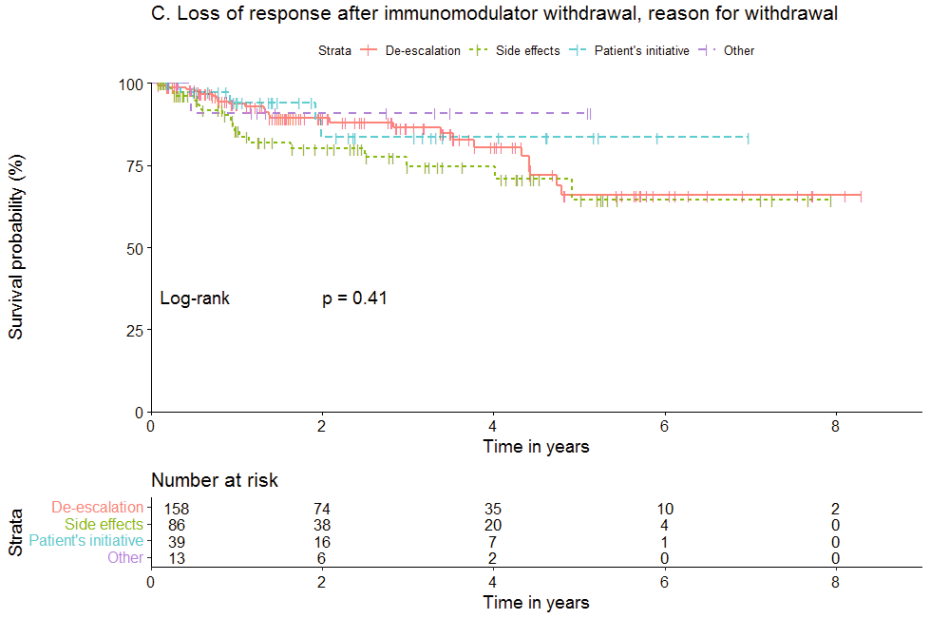
(sub)group	Events IMM withdrawal n (%)	Events IMM continuation n (%)	aHR	95%CI Lower limit	95%CI Upper limit
IFX	72 (34.8)	130 (61.6)	0.95	0.66	1.36
ADA	38 (42.7)	64 (59.8)	1.02	0.62	1.68
CD	74 (35.6)	137 (61.2)	0.94	0.68	1.31
UC	36 (40.9)	57 (60.6)	0.94	0.55	1.60
Naïve	81 (36.3)	124 (59.6)	1.20	0.84	1.70
ALL Patients	110 (37.2)	194 (61.0)	0.95	0.71	1.26

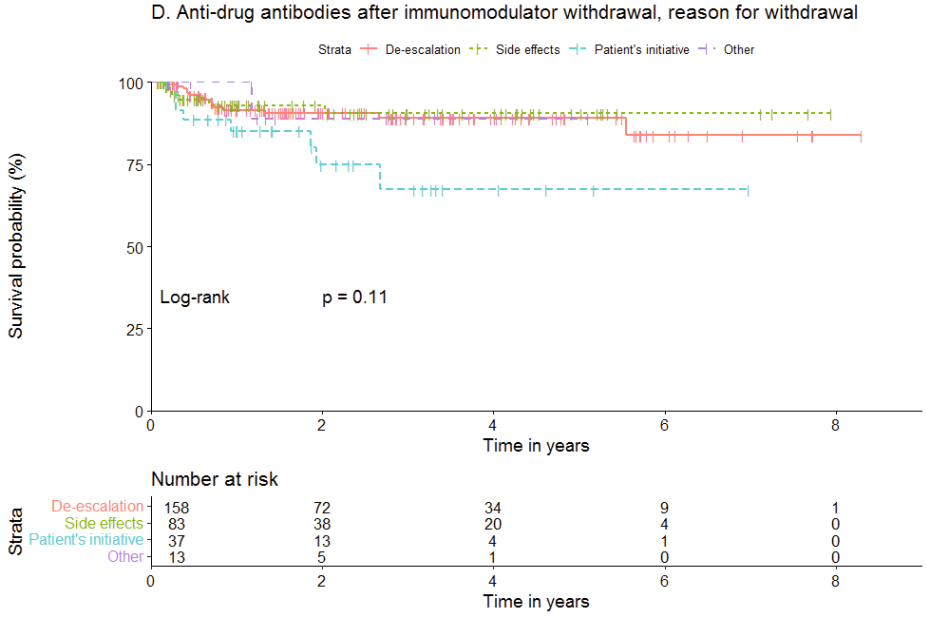
Supplementary Figure 1. Flow diagram of the selection process.



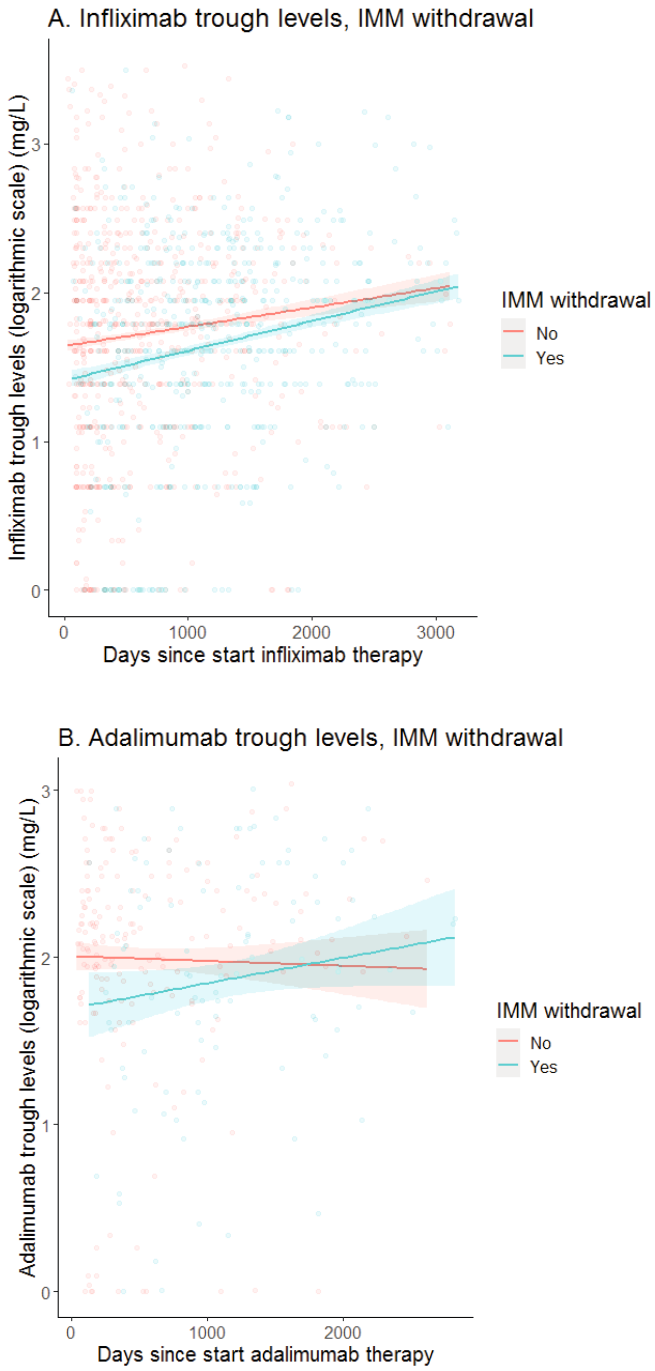
Supplementary Figure 2. Kaplan Meier curves. Incidence of loss of response (A) and anti-drug antibody detection (B) after immunomodulator withdrawal, stratified for duration of combination therapy. Incidence of loss of response (C) and anti-drug antibody detection (D) after immunomodulator withdrawal, stratified for reasons for withdrawal.

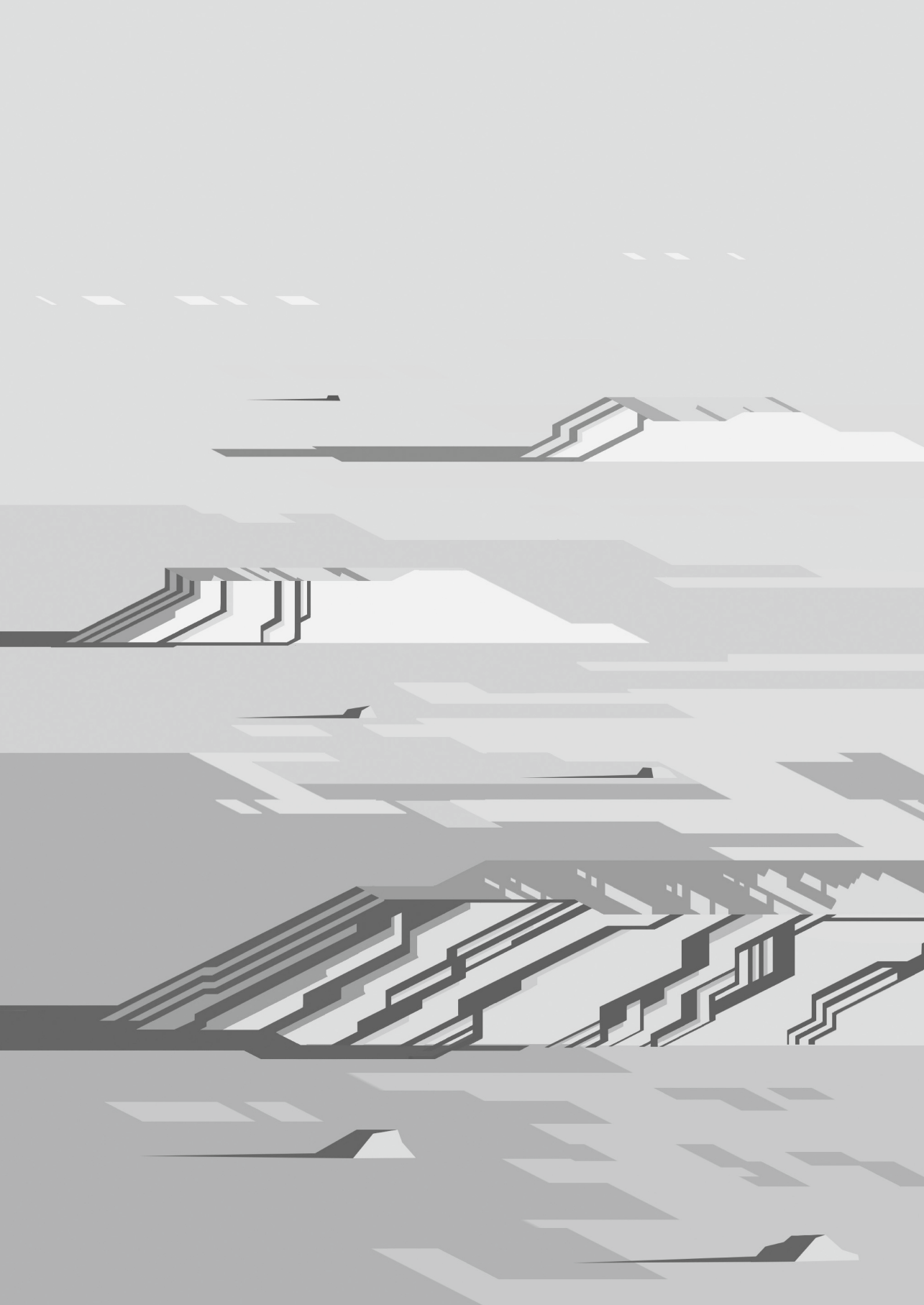



C. Loss of response after immunomodulator withdrawal, reason for withdrawal
Strata De-escalation Side effects Patient's initiative Other
Survival probability (%)
100
75
50
25
0
Log-rank p = 0.41
0 2 4 6 8
Time in years
Number at risk
Strata
De-escalation 158 74 35 10 2
Side effects 86 38 20 4 0
Patient's initiative 39 16 7 1 0
Other 13 6 2 0 0
0 2 4 6 8
Time in years


D. Anti-drug antibodies after immunomodulator withdrawal, reason for withdrawal
Strata De-escalation Side effects Patient's initiative Other
Survival probability (%)
100
75
50
25
0
Log-rank p = 0.11
0 2 4 6 8
Time in years
Number at risk
Strata
De-escalation 158 72 34 9 1
Side effects 83 38 20 4 0
Patient's initiative 37 13 4 1 0
Other 13 5 1 0 0
0 2 4 6 8
Time in years

Supplementary Figure 3. Association of infliximab (A) and adalimumab (B) trough levels with anti-TNF treatment duration after IMM withdrawal.





Chapter 5

Loss-of-response to anti-TNFα depends on treatment duration in patients with inflammatory bowel disease

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Aliment Pharmacol Ther. 2021 Nov;54(10):1298-1308.

Abstract

Background
Inflammatory bowel disease (IBD) is often managed with anti-tumour necrosis factor-α therapy (anti-TNFα), but treatment efficacy is compromised by high annual rates of loss-of-response (13-21% per patient-year).

Aims
We assessed whether the incidence of loss-of-response decreases with longer treatment duration.

Methods
This was a multicentre, retrospective cohort study of patients with ulcerative colitis (UC) or Crohn's disease (CD) who received anti-TNFα for at least 4 months between 2011-2019. We studied the incidence of loss-of-response as a function of treatment duration, employing parametric survival modelling. Predictors of loss-of-response were identified by Cox regression analysis. Secondary outcomes included overall anti-TNFα discontinuation and dose escalation.

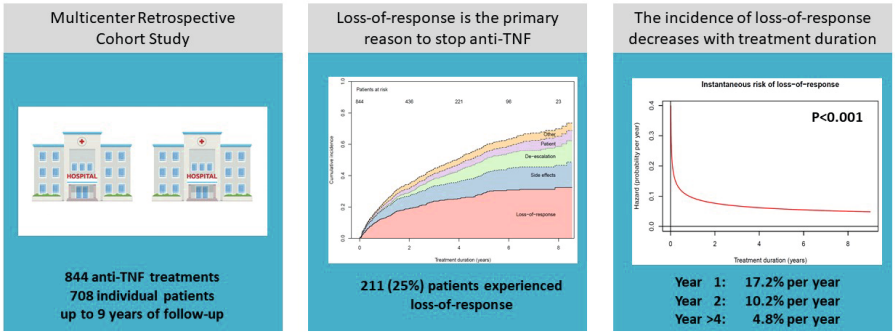
Results
We included 844 anti-TNFα treatment episodes in 708 individuals. Loss-of-response occurred in 211 (25.0%) episodes, with anti-drug antibodies detected in 66 (31.3%). During the first year, the incidence of loss-of-response was threefold higher than after four years of treatment (17.2% versus 4.8% per patient-year, p<0.001). The incidence of anti-TNFα discontinuation (28.6% versus 14.0% per patient-year, p<0.001) and dose escalations (38.0% versus 6.8% per patient-year, p<0.001) also decreased significantly from the first year to after four years, respectively. Predictors of loss-of-response included UC (versus CD, adjusted hazard ratio [aHR] 1.53, 95%CI 1.10 – 2.15) and, among patients with CD, stricturing or penetrating disease (aHR 1.68, 95% CI 1.15 – 2.46) and male sex (aHR 0.55, 95% CI 0.38–0.78). Immunomodulators were protective of loss-of-response with anti-drug antibodies (aHR 0.42, 95%CI 0.24 – 0.74).

Conclusions
Patients with sustained benefit to anti-TNFα after 2 years are at low risk of subsequent loss-of-response.

Keywords
Infliximab, adalimumab, ulcerative colitis, Crohn's disease

Graphical Abstract

Loss-of-response to anti-TNFα critically depends on treatment duration in patients with inflammatory bowel disease



Schultheiss JPD, Mahmoud R, et al. *Aliment. Pharmacol. Ther.*

AP&T

5

Introduction

Anti-tumour necrosis factor α (anti-TNFα) agents are widely used as maintenance treatment for patients with inflammatory bowel disease (IBD). After successful induction of remission, the risk of a subsequent loss-of-response to anti-TNFα has been estimated to be as high as 13-21% per patient-year, mostly based on studies with less than two years of follow-up.[1–4] In clinical practice however, anti-TNFα treatment is frequently continued much longer with, anecdotally, favourable long-term outcomes. Quantitative characterisation of long-term efficacy might help to balance the benefits of prolonged treatment against the risks of infections and malignancies, as well as treatment costs.[5–7] We hypothesised that although the yearly risk of treatment failure is relatively high immediately after anti-TNFα initiation, it is likely to decrease with longer treatment duration.

We conducted a large, multicentre, retrospective cohort study evaluating nine years of anti-TNFα treatment in patients with IBD. Our primary aim was to assess whether the incidence of loss-of-response – defined as drug discontinuation because of disease activity – declines with longer treatment duration. Secondary aims were to identify predictors of loss-of-response (with and without anti-drug antibodies), and to define the time-dependent risk of overall drug discontinuation and anti-TNFα dose intensifications.

Methods

Design

This was a multicentre, retrospective cohort study of patients with IBD receiving anti-TNFα maintenance treatment in a general hospital (St. Antonius Hospital Nieuwegein) and a referral centre (University Medical Centre Utrecht) in the Netherlands. A data query in databases of the gastroenterology departments and hospital pharmacies (with complete data available from 2011 onwards) was performed. We identified all adult IBD patients with at least one prescription for infliximab or adalimumab between 01.01.2011 and 01.01.2019, using ICD-10 codes for the IBD diagnosis and ATC codes for medication.

Individual charts were reviewed for the following inclusion criteria: an established diagnosis of Crohn's disease (CD) or ulcerative colitis (UC), at least one year of follow-up for treatment of IBD at the participating site, and at least one anti-TNFα treatment episode that could be included in the analysis. Treatment episodes were included if the first dose of anti-TNFα was administered after 01.01.2011 and before 01.01.2019, and the duration of treatment was at least four months. We excluded patients with IBD-unclassified and patients treated only with golimumab or certolizumab-pegol during the study period, due to small sample sizes. Treatment episodes initiated more than four months before the patient reached the age of 18 were excluded. This was necessary to reduce selection bias, as patients who started anti-TNFα during childhood were only identified by our search strategy if the anti-TNFα

was continued after transition to the adult gastroenterology department (i.e. patients with longer treatment duration).

In case individual patients were treated repeatedly with anti-TNFα compounds during the study period, all treatment episodes that met the eligibility criteria were analysed. Switching to other anti-TNFα agents or restarting anti-TNFα after a drug holiday of more than 90 days was categorised as a new treatment episode.

Data collection and definitions

We collected data on demographics, disease characteristics, prior medical treatment, IBD-related surgical interventions, and comorbidity (including primary sclerosing cholangitis [PSC] and rheumatologic comorbidities). For included patients, data from all anti-TNFα treatment episodes were recorded, including episodes that were not eligible for the primary analysis (in order to account for any prior anti-TNFα exposure). We noted the date of first anti-TNFα administration, indication for anti-TNFα (luminal versus perianal disease), and whether and when the anti-TNFα agent was withdrawn. Reasons for anti-TNFα discontinuation were classified as primary non-response, loss-of-response, side-effects, de-escalation, patient's decision or 'other'. De-escalation was defined as elective anti-TNFα withdrawal in patients having achieved durable remission.[8] Primary non-response was defined as discontinuation of anti-TNFα because of disease activity within four months of anti-TNFα initiation. Loss-of-response was defined as anti-TNFα discontinuation because of disease activity after four months of treatment. Disease activity was based on the physician's interpretation (usually based on symptoms with at least one adjunctive endoscopic, radiographic or biochemical finding). Prior anti-TNFα failure was defined as primary non-response or loss-of-response in any previous treatment episode.

Dose escalations, defined as any increase in the dose or decrease of the dosing interval from standard regimens (5mg/kg every eight weeks for infliximab, 40mg every two weeks for adalimumab), and corresponding dates were recorded. Prior immunomodulator failure (azathioprine, 6-mercaptopurine, thioguanine and methotrexate) was defined as persisting disease activity despite immunomodulator use for at least three months before the first anti-TNFα administration. Concomitant immunomodulator use during treatment episodes was recorded, with dates of discontinuation and/or (re)initiation if applicable. Any (interruption in) use of immunomodulators of less than 30 days was ignored. Baseline immunomodulator use was defined as either initiation of an immunomodulator within 30 days, or continuation of the immunomodulator for at least 30 days, following anti-TNFα initiation.

Anti-TNFα trough levels and anti-drug antibodies were recorded, if available. Anti-drug antibodies were typically only measured in patients with anti-TNFα trough levels <1.0mg/L. Therefore, antibodies were considered absent if the trough level was ≥1.0mg/L. Of note, the standard of care at both participating sites is best characterised by reactive therapeutic

drug monitoring (TDM). CRP and faecal calprotectin levels were recorded at the start of anti-TNFα (available in 71% and 31%, respectively), and at the time of anti-TNFα discontinuation (maximum of six weeks prior to start/stop).

Data from endoscopic procedures performed between six months before the start until six months after the end of a treatment episode were extracted from endoscopy reports. The most proximal bowel segment examined and degree of disease activity (none, mild, moderate, severe) in the most severely affected bowel segment were noted. Mucosal healing was defined as absence of endoscopically visible inflammation. Procedures performed at least 90 days after anti-TNFα initiation were analysed as potential predictors of loss-of-response. Endoscopies performed less than 90 days before anti-TNFα discontinuation were considered to indicate a concurrent outcome of interest (e.g. loss-of-response), and were excluded from the analyses aimed to identify predictors of future loss-of-response.

Statistical analysis

Descriptive characteristics were reported according to the distribution of the data, with continuous parameters noted as medians with interquartile ranges (IQR) unless stated otherwise. Kaplan-Meier curves are presented with log-rank test for significance. We corrected for multiple comparisons with the Benjamini-Hochberg procedure to decrease the false discovery rate (FDR). Time-at-risk started at anti-TNFα maintenance therapy (four months after anti-TNFα initiation). If the outcome of interest did not occur, patients were censored at anti-TNFα discontinuation, last follow-up at the study site or end of the study period (01.12.2019).

The incidence rate per patient-year of all outcomes was calculated for different time spans. To formally test whether the incidence of outcomes declined or increased with treatment duration, we performed parametric survival modelling with the Wald test for significance (**Supplementary methods**). Subgroup analyses were performed in patients with UC or CD. Sensitivity analyses were performed for patients without prior anti-TNFα exposure (resulting in only one episode per individual patient), and for patients with at least one year of treatment, as high rates of anti-TNFα discontinuation in the first year might be attributed in part to unintentional inclusion of primary non-responders (only excluded from this study if the anti-TNFα was withdrawn within four months).

To identify predictors of loss-of-response, a Cox regression model was constructed, accounting for multiple treatment episodes per patient (details in **Supplementary methods**). Due to the amount of missing data, pharmacokinetic and biochemical parameters were not incorporated in the regression models. Mucosal healing was analysed as a time-varying covariate. Immunomodulators were primarily analysed by baseline use, and additional analysis was performed with immunomodulator use as a time-changing covariate, with a 90-day delay after starting/stopping an immunomodulator. Separate analyses were

performed for the outcomes of loss-of-response with and without anti-drug antibodies, and for the subgroups of patients with UC or CD and anti-TNFα naïve patients.

All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A p-value of <0.05 was considered significant.

Study Oversight

This study was carried out in accordance with the ethical guidelines of the Institutional Review Board of the University Medical Centre Utrecht. The study received exempt status from the Institutional Review Board due to the observational design**.**

Results

Cohort characteristics

The eligibility criteria were fulfilled in 708 individual patients, yielding a total of 844 treatment episodes and 2270 patient-years of follow-up **(Table 1, Supplementary Figure 1).** The median treatment duration was 2.4 years (IQR 1.2 – 4.4) per episode, and treatment duration was longer than four years in 247 (29.3%) episodes (**Table 2**). Anti-TNFα trough levels and/or anti-drug antibodies were measured at least once in 681 (80.7%) treatment episodes.

Several characteristics differed significantly between patients with UC and CD, including a lower frequency of smoking, older age at diagnosis (**Table 1**), older age at anti-TNFα initiation, a shorter treatment duration and a lower frequency of prior anti-TNFα failure (**Table 2**) in those with UC. Notably, patients with UC more frequently used infliximab (and less often adalimumab) and were more often prescribed combination therapy.

Irrespective of IBD phenotype, infliximab was more often combined with immunomodulators at anti-TNFα initiation, as compared to adalimumab (79.0% versus 58.6%, p<0.001). During follow-up, 285 (47.9%) patients discontinued the immunomodulator, after a median of 0.9 years (IQR 0.6 – 2.1).

Incidence of loss-of-response

Anti-TNFα discontinuation because of loss-of-response occurred in 211 (25.0%) episodes (**Figure 1**). Patients who experienced loss-of-response, did so after a median of 11.2 (IQR 3.8 – 27.2) months since the start of the maintenance phase (i.e. four months after anti-TNFα initiation). The overall incidence of loss-of-response was 9.3% (95% CI 8.1 – 10.6%) per patient-year.

Table 1. Baseline Characteristics

	Total cohort (N=708)	**CD (N=532)**	**UC (N=176)**	**p-value**
Female Sex	378 (53.4)	292 (54.9)	86 (48.9)	0.16
BMI	25.1 (22.3 – 28.7)	25.1 (22.3 – 28.7)	25.3 (22.2 – 28.9)	0.61
Smoking	179 (26.2)	162 (23.8)	17 (10.0)	**<0.001***
Concomitant PSC	24 (3.4)	16 (3.0)	8 (4.5)	0.33
Rheumatologic comorbidity	102 (14.4)	83 (15.6)	19 (10.8)	0.12
Age at IBD diagnosis	26.1 (20.6 – 38.8)	24.9 (20.0 – 37.3)	29.8 (22.9 – 43.8)	**<0.001***
Medication exposure prior to first anti-TNF				
Systemic steroids	543 (82.4)	286 (79.3)	157 (91.3)	**<0.001***
Thiopurines	596 (85.0)	452 (86.1)	144 (81.8)	0.17
Methotrexate	95 (13.6)	84 (16.0)	11 (6.2)	**0.001***
Disease behavior				
Inflammatory (B1)	-	235 (44.2)	-	-
Stricturing (B2)		201 (37.8)		
Penetrating (B3)		95 (17.9)		
Disease location				
Ileal (L1)	-	152 (28.6)	-	-
Colonic (L2)		99 (18.6)		
Ileocolonic (L3)		276 (51.9)		
Isolated upper GI (L4)		5 (0.9)		
L1/L2/L3 + upper GI (L4)		62 (11.8)		
Perianal disease	-	177 (33.3)		-
Disease extent	-	-		-
Proctitis (E1)			13 (7.4)	
Left-sided (E2)			61 (34.7)	
Extensive (E3)			102 (58.0)	

Missing data: BMI (n=36), Smoking (n=26), Disease behavior (n=1), upper GI involvement (n=2). Prior exposure to steroids (n=49), thiopurines (n=7), MTX (n=8). *Significant at p<0.05.

Table 2. Treatment characteristics

	Treatment episodes (n=844)	CD (n=636)	UC (n=208)	p-value
Treatment episode				**0.05***
First anti-TNF	555 (65.8)	402 (63.2)	153 (73.6)	
Second anti-TNF	225 (26.7)	180 (28.3)	45 (21.6)	
Third anti-TNF	57 (6.8)	48 (7.5)	9 (4.3)	
Fourth anti-TNF	7 (0.8)	6 (0.9)	1 (0.5)	
Prior anti-TNF failure	152 (18.0)	130 (20.4)	22 (10.6)	**0.001***
Primary non-response	21 (2.5)	18 (2.8)	3 (1.4)	0.26
Loss of response	137 (16.2)	116 (18.2)	21 (10.1)	**0.006***
Treatment duration	2.4 (1.2 – 4.4)	2.6 (1.3 – 4.5)	2.1 (0.9 – 3.7)	**0.001***
Disease duration at start	4.6 (1.4 – 12.6)	4.9 (1.3 – 14.1)	4.1 (1.6 – 9.6)	0.10
Age at start	36.2 (26.5 – 51.7)	35.5 (25.9 – 50.5)	38.0 (28.8 – 53.2)	**0.006***
Anti-TNF agent				**0.002***
Infliximab	518 (61.4)	371 (58.3)	147 (70.7)	
Adalimumab	326 (38.6)	265 (41.7)	61 (29.3)	
Prior IMM failure[1]	311 (56.4)	222 (55.8)	89 (58.2)	0.61
Any concomitant IMM use				
At start anti-TNF	638 (75.9)	465 (73.5)	173 (83.2)	**0.005***
Withdrawn during the episode[2]	598 (71.1)	432 (68.2)	166 (79.8)	**0.001***
	285 (47.9)	208 (48.4)	77 (46.7)	0.71
Added during the episode[3]	42 (17.9)	33 (16.8)	9 (23.1)	0.35
Prior IBD-related surgery[4]	180 (21.3)	179 (28.1)	1 (0.5)	**<0.001***

1. Subgroup of anti-TNF naïve patients (n=555) 2. Subgroup of patients with IMM at start (n=598) with anti-TNF continued at least 30 days after IMM withdrawal. 3. Subgroup of patients without immunomodulator at start anti-TNF (n=243). 4. Bowel resections, stricturoplasty or fecal diversion. **Missing data:** Concomitant IMM use (n=3), Prior IMM failure (n=4). *Significant at p<0.05.

The incidence rates of anti-TNFα discontinuation with corresponding reasons are presented in **Table 3**. The incidence of loss-of-response was as high as 17.2% per patient-year (95% CI 13.7 – 21.2) during the first year of treatment, but declined more than threefold to 4.8% per patient-year (95% CI 3.1 – 7.2) after four years. Indeed, the hazard of loss-of-response dropped significantly with longer treatment duration in all patients (**Figure 1b**, p<0.001), in patients with UC, patients with CD (both p<0.001) and in the sensitivity analyses of patients with at least one year of treatment (p=0.002) and anti-TNFα naïve patients (p<0.001). The incidences of loss-of-response during the first year, second year, and after four years were 29.5%, 8.9%, 7.4% per patient-year for UC, 13.4%, 10.5%, and 4.2% for CD and 18.4%,

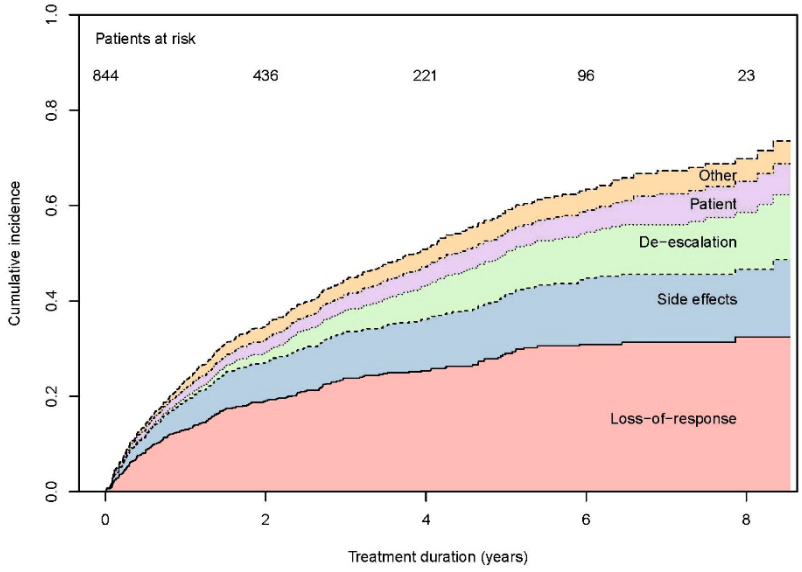
9.4% and 3.7% for anti-TNFα naïve patients, respectively. Of note, the incidence of loss-of-response in patients with UC continued to decrease beyond six months of treatment (p<0.001), but this was no longer significant beyond 1 year (p=0.34).

Anti-drug antibodies were detected at any point during the treatment in 66 (31.3%) episodes with loss-of-response. The last available trough level was ≤1.0mg/L in 53 (80%) episodes and median antibody titer was 255AU/mL (IQR 82 – 755, **Supplementary Table 1**). The remaining 145 (68.7%) cases were classified as loss-of-response *without* anti-drug antibodies. In these patients, the most recent median trough level (available in 114, 78.6%) was within the therapeutic window (infliximab: 6.0mg/L, IQR 3.9 – 8.5; adalimumab: 7.7mg/L, IQR 5.0 – 12.2, **Supplementary Table 1**). Of note, faecal calprotectin, but not CRP, was significantly higher among patients with loss-of-response *without* anti-drug antibodies (**Supplementary Table 1**, p=0.03).

Again, the incidences of loss-of-response both with and without anti-drug antibodies declined with longer treatment duration (p=0.003 and p<0.001 respectively, **Supplementary Table 2**). Results were similar in the subgroup and sensitivity analyses, although in patients with UC and patients with more than one year of follow-up, the decreasing trends in loss-of-response *with* anti-drug antibodies were not significant (p=0.07 and p=0.14, respectively).

Figure 1. A) Cumulative incidence of anti-TNFα discontinuation with corresponding reasons, Aalen Johansen curve accounting for competing events. B) Hazard function of loss-of response (parametric model) showing significant decrease in hazard over time (p<0.001).

A



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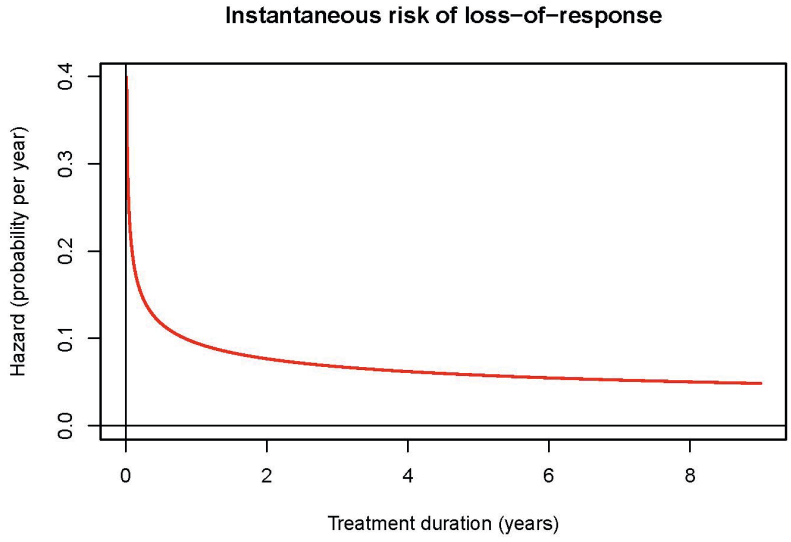


Table 3. Summary of incidence rates of LOR and anti-TNF discontinuation by treatment duration

Discontinuation of anti-TNF	**Cumulative incidence, n (%)**	**Incidence rate, % per patient-year (95% confidence interval)**					**Trend (p-value)[1]**
Patients at risk	**N=844**	**4months – 1year N=844**	**1-2 years N=684**	**2-3 years N=477**	**3-4 years N=343**	**>4 years N=247**	
All reasons	**428** (50.7)	**28.6** (24.1 – 33.7)	**20.8** (17.3 – 24.9)	**13.0** (9.7 – 17.0)	**14.4** (10.3 – 19.5)	**14.0** (10.9 – 17.7)	**Decrease* (p<0.001)**
LOR	**211** (25.0)	**17.2** (13.7 – 21.2)	**10.2** (7.7 – 13.1)	**5.6** (3.6 – 8.4)	**6.7** (4.0 – 10.4)	**4.8** (3.1 – 7.2)	**Decrease* (p<0.001)**
Side effects	**93** (11.0)	**6.9** (4.8 – 9.6)	**5.1** (3.4 – 7.3)	**2.2** (1.0 – 4.2)	**2.1** (0.7 – 4.6)	**2.8** (1.5 – 4.7)	**Decrease* (p=0.001)**
De-escalation	**58** (6.9)	**0.8** (0.2 – 2.0)	**1.8** (0.8 – 3.2)	**3.7** (2.1 – 6.1)	**3.2** (1.4 – 6.0)	**4.0** (2.5 – 6.2)	**Increase* (p<0.001)**
Patients initiative	**35** (4.1)	**2.4** (1.2 – 4.1)	**1.4** (0.6 – 2.8)	**0.7** (0.2 – 2.1)	**1.7** (0.6 – 4.1)	**1.4** (0.6 – 2.9)	Decrease (p=0.14)
Other	**31** (3.7)	**1.4** (0.6 – 2.9)	**2.5** (1.3 – 4.1)	**0.7** (0.2 – 2.1)	**0.7** (0.1 – 2.5)	**1.0** (0.3 – 2.3)	Decrease (p=0.21)

Note that the intervals of treatment duration have different lengths, but incidence rates are reported as % per patient-year and can be compared directly. 1) Based on parametric survival modelling with Wald test for significance of decreasing/increasing versus constant hazard. *Significant at p<0.05.

Predictors of loss-of-response

Univariable analyses revealed a significantly higher incidence of loss-of-response in UC patients versus CD patients (**Figure 2A**, p=0.02). Baseline immunomodulator use (**Figure 2B,** p=0.16), use of adalimumab compared with infliximab (**Figure 2C**, p=0.30), or year of inclusion did not significantly predict loss-of-response (**Figure 2D**, p=0.06). Baseline CRP and faecal calprotectin did not differ significantly between those who did and did not experience loss-of-response during follow-up (median CRP 11.5 versus 7.9mg/L, p=0.06, median faecal calprotectin 1377 versus 942 µg/g, p=0.20).

On multivariable analysis, patients with UC were at higher risk of loss-of-response compared with patients with CD (adjusted hazard ratio [aHR] 1.53, 95% CI 1.10 – 2.15, **Table 4**). In the sensitivity analysis of patients without prior anti-TNFα exposure, this remained significant. Among anti-TNFα naïve patients, higher age at diagnosis (aHR 1.01 per year, 95%CI 1.00 – 1.03, p=0.03) or higher age at starting anti-TNFα (aHR 1.01 per year, 95%CI 1.00 – 1.02, p=0.08, trend) were also associated with loss-of-response but could not be assessed simultaneously due to collinearity (Pearson R^2: 0.66, p<0.001).

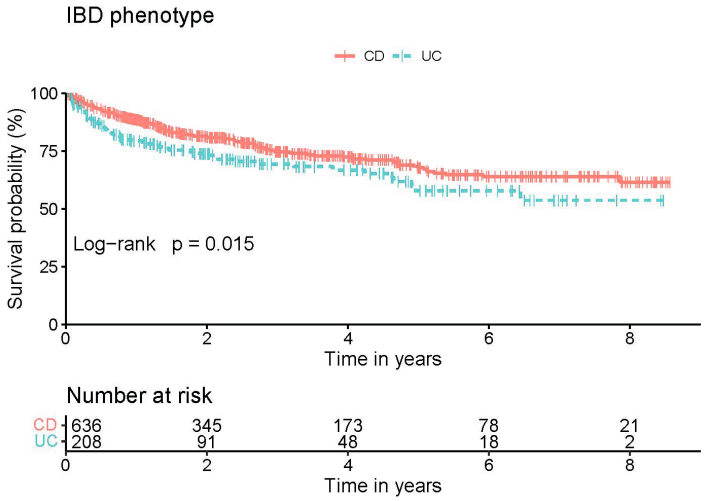
In the subgroup of patients with CD, stricturing or penetrating disease was associated with higher risk of loss-of-response (aHR 1.68, 95% CI: 1.15 – 2.46) (**Supplementary Table 3**), while male sex was protective (aHR 0.55, 95%CI 0.38 – 0.78). No predictors were identified in patients with UC (**Supplementary Table 4**).

PSC was a significant independent predictor of loss-of-response *with* anti-drug antibodies (**Supplementary Table 5,** aHR 3.06, 95%CI 1.05 – 8.91), while male sex (aHR 0.53, 95%CI 0.31 – 0.93) and baseline immunomodulator use were protective (aHR 0.42, 95CI: 0.24 – 0.74). The risk of loss-of-response *without* antibodies was significantly higher among patients with UC, compared with CD (aHR 1.57, 95% CI 1.07 – 2.30, **Supplementary Table 6**).

Immunomodulators were still not significantly protective of loss-of-response after adjusting for immunomodulator withdrawal or (re)initiation during follow-up in all patients (aHR 1.02, 95CI 0.77 – 1.35), nor in the subgroups of patients without prior anti-TNFα exposure, patients with CD or UC (data not shown). Furthermore, in this time-varying analysis, immunomodulators were no longer protective of loss-of-response *with* anti-drug antibodies (aHR 0.67, 95%CI 0.40 – 1.15), and were associated with higher risk of loss-of-response *without* anti-drug antibodies (aHR 1.47, 95%CI 1.02 – 2.12).

Figure 2. Incidence of loss-of-response (Kaplan Meier curves), subgroups analyses per A) IBD phenotype, B) baseline immunomodulator use, C) anti-TNF agent and D) Year of inclusion.

A



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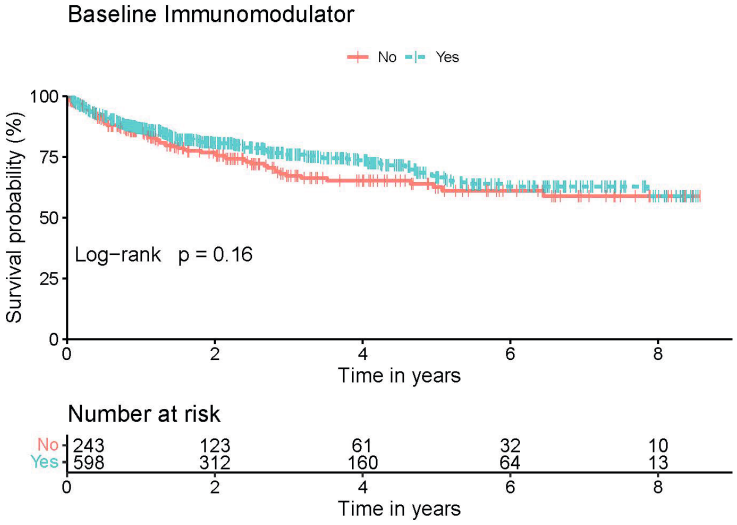

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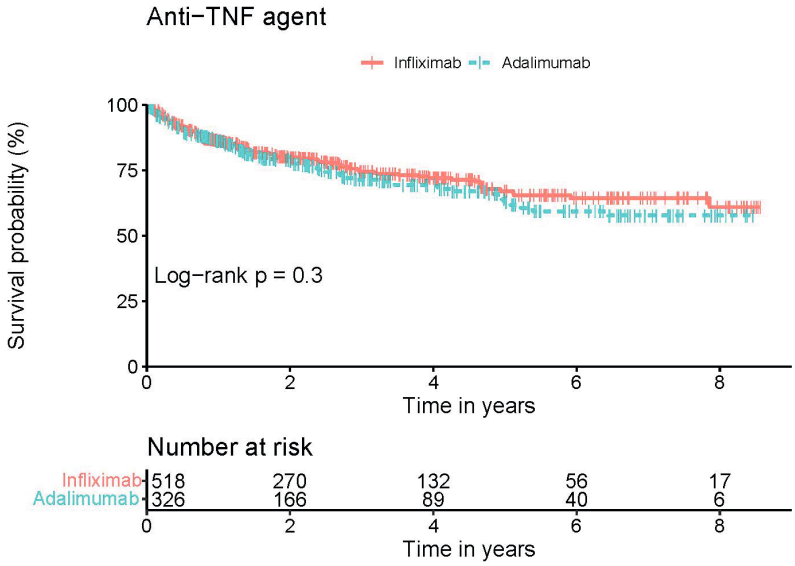

Anti−TNF agent
Infliximab
Adalimumab
Survival probability (%)
100
75
50
25
0
Log−rank p = 0.3
0
2
4
6
8
Time in years
Number at risk
Infliximab 518 270 132 56 17
Adalimumab 326 166 89 40 6
0
2
4
6
8
Time in years

D

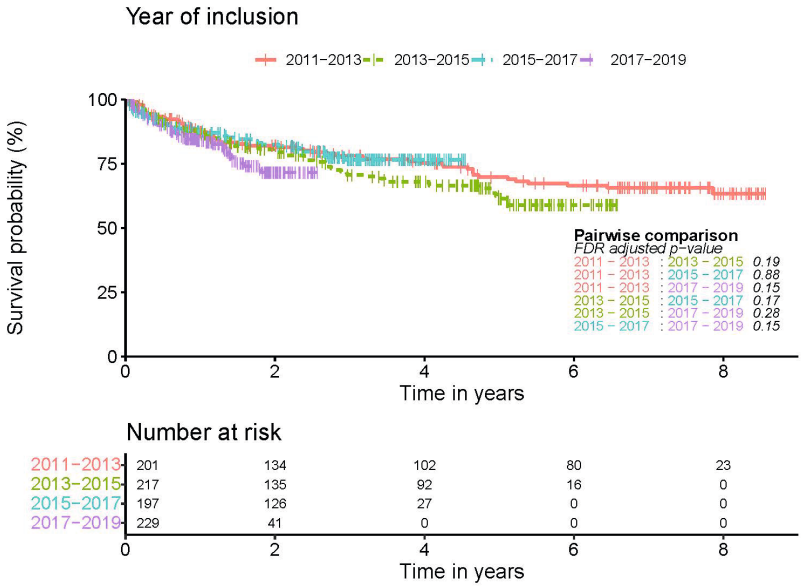

Year of inclusion
2011−2013
2013−2015
2015−2017
2017−2019
Survival probability (%)
100
75
50
25
0
Pairwise comparison
FDR adjusted p−value
2011 − 2013 : 2013 − 2015 0.19
2011 − 2013 : 2015 − 2017 0.88
2011 − 2013 : 2017 − 2019 0.15
2013 − 2015 : 2015 − 2017 0.17
2013 − 2015 : 2017 − 2019 0.28
2015 − 2017 : 2017 − 2019 0.15
0
2
4
6
8
Time in years
Number at risk
2011−2013 201 134 102 80 23
2013−2015 217 135 92 16 0
2015−2017 197 126 27 0 0
2017−2019 229 41 0 0 0
0
2
4
6
8
Time in years

Table 4. Cox regression analysis for loss-of-response (all patients).

	Univariable HR (95% CI)	p-value	**Multivariable** HR (95% CI)	p-value
Male sex	0.82 (0.61 – 1.08)	0.16	0.76 (0.57 – 1.02)	0.07
UC (versus CD)	**1.50 (1.09 – 2.05)**	**0.01***	**1.53 (1.10 – 2.15)**	**0.01***
Smoking	0.84 (0.60 – 1.18)	0.31	0.96 (0.68 – 1.37)	0.82
BMI	0.99 (0.96 – 1.02)	0.49	0.99 (0.96 – 1.02)	0.47
PSC	1.60 (0.84 – 3.07)	0.15	1.73 (0.89 – 3.36)	0.10
Age at diagnosis	1.01 (1.00 – 1.02)	0.07	1.01 (1.00 – 1.02)	0.07
Age at start anti-TNF[2]	1.01 (1.00 – 1.02)	0.19	NA	
Adalimumab (versus Infliximab)	1.15 (0.87 – 1.52)	0.34	1.15 (0.85 – 1.55)	0.38
Mucosal healing[1]	0.88 (0.48 – 1.61)	0.67	0.79 (0.42 – 1.46)	0.45
Prior anti-TNF failure	1.13 (0.81 – 1.58)	0.47	1.20 (0.83 – 1.73)	0.34
Baseline immunomodulator use	0.80 (0.60 – 1.09)	0.16	0.80 (0.58 – 1.09)	0.16

Multivariable model corrected for disease duration. 1) Entered as a time changing covariate. 2) not entered in the multivariable model due to collinearity with age at diagnosis. *Significant at p<0.05.

Anti-TNFα discontinuation

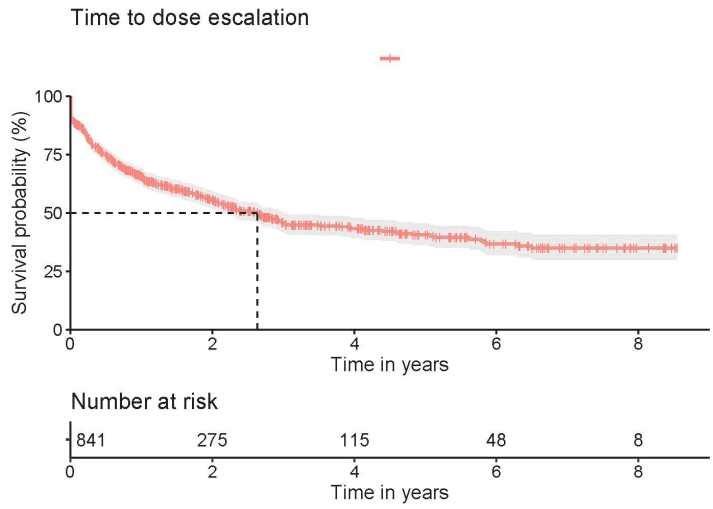
Overall, anti-TNFα discontinuation occurred in 428 (50.7%) treatment episodes, with a median drug survival of 3.9 years (95% CI 3.3 – 4.4) since the start of the maintenance phase. Longer treatment duration was associated with decreased incidence rates of anti-TNFα discontinuation (28.6% in the first year to 14.0% per patient-year beyond four years, p<0.001, **Table 3**). Regarding discontinuation reasons other than loss-of-response, longer treatment duration was associated with lower rates of anti-TNFα withdrawal for side effects (p=0.001) and higher rates of elective anti-TNFα withdrawal as a de-escalation strategy (p<0.001, **Table 3**). These findings were similar in patients with UC and CD, as well as in patients with at least one year of anti-TNFα treatment and anti-TNFα naïve patients. However, in patients with UC, the decrease in anti-TNFα discontinuation for side effects and the increase of anti-TNFα discontinuation for remission did not reach statistical significance (p=0.09 and p=0.07, respectively). Among patients who stopped anti-TNFα, CRP, faecal calprotectin and anti-drug antibody titers were significantly higher among those who stopped anti-TNFα due to loss-of-response, compared with anti-TNFα discontinuation for any other reason (**all p<0.001, Supplementary Table 7)**, while infliximab (p=0.02) and adalimumab (p=0.01) trough levels were significantly lower.

Dose escalations

Dose escalation occurred in 386 (45.9%) treatment episodes, of which 76 (19.7%) occurred within four months following anti-TNFα initiation (**Figure 3**). Thereafter, the

incidence rate of dose escalation was 38.0% (95% CI 32.3% - 44.4%) per patient-year between four months and one year, and decreased significantly to 6.8% (95% CI 3.9% – 10.8%) beyond four years of treatment duration (**Supplementary Table 8**, p<0.001). In 222 (71.6%) out of 310 dose escalations during follow-up, TDM was performed within the four months prior to the dose escalation (median trough level of 1.6mg/L and 3.8mg/L for infliximab and adalimumab, respectively, **Supplementary Table 9).** Dose escalation was followed by loss-of-response in 130 (33.7%) episodes (aHR 4.97, 95%CI 3.64 – 6.78), while in 58 (15.0%) episodes, patients were able to return to the standard dosing regimen during follow-up. In the subgroup and sensitivity analyses of patients with UC, patients with CD, patients with more than one year follow-up and anti-TNFα naïve patients, the incidence of dose-escalations also decreased significantly over time (data not shown, all p<0.001).

Figure 3. Kaplan Meier curve displaying the incidence of anti-TNFα dose escalation.



Discussion

Based on a large retrospective cohort of 844 episodes of anti-TNFα treatment, we observed that after four years of anti-TNFα treatment, the incidence of loss-of-response was more than threefold lower than during the first year. Additionally, a significant decrease over time was noted for the incidences of anti-TNFα discontinuation, anti-TNFα discontinuation because of side-effects, and dose escalations. Not surprisingly, the incidence of elective anti-TNFα withdrawal as a de-escalation strategy increased with longer treatment duration. Taken together, our findings indicate that patients with IBD with sustained benefit to anti-TNFα for more than approximately two years, represent a selected population with a favourable efficacy-tolerability balance to anti-TNFα.

A meta-analysis in patients with CD with a mean follow-up of 1.8 years reported an incidence of loss-of-response to anti-TNFα of up to 20.9% per patient-year.[1] Of note, prior studies employed heterogeneous definitions for loss-of-response, ranging from symptom scoring to need for surgical intervention.[1,2] The substantially lower overall incidence of loss-of-response in our study (9.6% per patient-year) can be partially explained by our longer follow-up. Furthermore, our definition of loss-of-response required anti-TNFα discontinuation, thereby excluding transient or mild disease activity during anti-TNFα therapy. Notably, dose escalations are often an effective first-line strategy in case of flares in real-world clinical practice,[9–11] and the incidence of dose escalations also decreased with longer treatment duration in our cohort.

It may seem intuitive that the incidence of loss-of-response declines with longer treatment duration.[3] However, this has not been assessed quantitatively as in our study, and this has several implications. From a biological perspective, our results imply that loss-of-response to anti-TNFα does not occur randomly. Instead, over time patients with a better response and tolerability are selected – either due to specific benefit from anti-TNFα treatment, or a milder IBD phenotype in general. From a clinical point of view, we provide detailed long-term outcomes of anti-TNFα treatment – which may aid clinicians to adequately inform patients on the benefits and risks of continued treatment beyond 1-2 years, for example when considering anti-TNFα withdrawal as a therapeutic de-escalation strategy.[8,12] Notably, longer duration of anti-TNFα use does not seem to protect from relapse after elective withdrawal of anti-TNFα.[13]

Several predictors of loss-of-response were identified in our cohort. In line with a recent retrospective study, UC patients were at higher risk of loss-of-response than patients with CD, with a high incidence of loss-of-response among UC patients within the first year.[14] Female patients were at an increased risk of loss-of-response *with* anti-drug antibodies, and at an increased risk for any loss-of-response among patients with CD. Female sex has previously been associated with shorter anti-TNFα treatment persistence and higher risk of side-effects in patients with IBD or rheumatologic conditions.[14–17] Our findings suggest that this might be related to immunogenicity. Notably, PSC was also associated with a higher risk of antibody-mediated loss-of-response, although this finding should be interpreted with caution given the small number of patients with PSC in our study. In contrast to prior studies – including long-term follow-up of the CALM study,[18] achieving mucosal healing did not prevent subsequent loss-of-response to anti-TNFα. However, our findings should primarily be regarded as exploratory analyses, as only 40.9% of patients underwent endoscopy during follow-up and our definition (absence of visible inflammation) was stricter than most prior studies.[19,20]

Immunomodulators protected from loss-of-response with anti-drug antibodies, in line with prior studies reporting decreased risks of loss-of-response and immunogenicity to anti-TNFα[21,22], as well as higher infliximab trough levels among patients receiving combination therapy.[23,24] Our findings additionally suggest against a relevant independent effect of the

thiopurine on the intestinal mucosa – as immunomodulators did not protect from loss-of-response without anti-drug antibodies. In line with a recent long-term observational study,[14] loss-of-response (regardless of anti-drug antibodies) was not significantly lower among patients receiving combination therapy. However, relatively few patients received monotherapy (likely highly selected on clinical grounds), and withdrawal and initiation of immunomodulators during maintenance treatment occurred frequently. Counterintuitively, accounting for changing immunomodulator use further diminished any protective effect of immunomodulators on loss-of-response. It is likely that patients perceived to be at low risk of loss-of-response would preferentially stop the immunomodulator during maintenance treatment, while only high risk patients would continue or (re)initiate the immunomodulator.

This study has several strengths. In general, our results, coming from a large cohort with meticulous data collection, substantially add to the existing literature on long-term maintenance treatment with anti-TNFα. The substantial sample size allowed us to precisely estimate incidence rates even beyond four years of treatment. In identifying predictors of loss-of-response, we accounted for potential confounders and assessed changes over time in immunomodulator use or achieving mucosal healing. Most importantly though, we focused on the dynamic aspects of long-term anti-TNFα treatment and detected a substantial change in incidences and reasons for anti-TNFα discontinuation with longer treatment duration.

As with all retrospective studies, several limitations of the current study need to be acknowledged. Faecal calprotectin, CRP levels and pharmacokinetic measurements were not available in all patients and were therefore only analysed descriptively. Limited misclassification of patients as having loss-of-response with versus without anti-drug antibodies may have occurred among the minority in whom trough levels or anti-drug antibodies were not measured shortly before loss-of-response. Loss-of-response was pragmatically distinguished from primary non-response by treatment duration (after versus before four months), but our sensitivity analysis confirmed that the risk of loss-of-response decreased beyond 1 year. Although our cohort is a mixed population of secondary and tertiary care patients, the generalizability is partially limited by exclusion of patients who started an anti-TNFα agent before adulthood. Finally, we reported several relevant predictors of loss-of-response, but none were identified within the smaller subgroup of patients with UC.

The therapeutic armamentarium for IBD is rapidly expanding with alternatives for anti-TNFα, including non-anti-TNFα biologicals and small molecules.[25,26] Current literature provides little guidance to clinicians for selecting the optimal therapy for individual patients, as only one head-to-head trial has been published and no drug-specific biomarkers are available.[27,28] For a chronic, life-long disease such as IBD, it is essential to not only characterise the initial treatment response but also to examine long-term outcomes. Our results coming from a nine-year retrospective analysis indicate that patients on long-term anti-TNFα treatment represent a distinct population with high clinical benefit and tolerability of maintenance treatment.

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Supplementary Methods

Parametric survival modelling

To formally test whether the incidence of outcomes declined over time, we constructed parametric survival models assuming a Weibull distribution to estimate the underlying hazard function, with the Wald test for a significant increase/decrease in the hazard with longer treatment duration. The goodness-of-fit of the models was determined graphically by comparing the cumulative hazard function of a non-parametric model to the parametric model.

Cox regression analysis

To identify predictors of loss-of-response, a multilevel Cox proportional hazards regression model was constructed, accounting for multiple treatment episodes per patient, and potential different baseline hazards for loss-of-response by employing a random intercept per patient.

The proportional hazards assumption was assessed for each variable using Schoenfeld residuals. Only disease duration violated this assumption, and was entered in the model as a stratum. For this purpose, the variable was categorised into quartiles. In case of relevant interdependency or collinearity (Pearson R-square >0.60) between two parameters, the most predictive parameter on univariable analysis was entered in the multivariable model. Otherwise, all relevant parameters were entered in the multivariable model.

Data on smoking were missing in 26 patients, on BMI in 36, on disease behaviour in one and on upper gastrointestinal involvement in two patients, and dose escalations in three. We assumed that these data were missing at random. Using the MICE package in R, we performed multiple imputation based on iterative (20 iterations) chained equations with sex, length, weight, disease, age at start, smoking status, BMI, anti-TNFα agent, treatment episode, disease duration, Nelson-Aalen estimate, mucosal healing, dose intensification, concomitant immunomodulator use, Montreal B classification and upper gastrointestinal involvement as potential predictors, creating 10 imputed datasets[1]. All regression models were developed in the 10 imputed datasets and the results were pooled employing Rubin's rule.[2]

Supplementary Methods References

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Supplementary Table 1. Biochemical parameters at the time of anti-TNF discontinuation (loss-of-response with versus without anti-drug antibodies)

	Loss-of-response With antidrug antibodies N=66	Loss-of-response without anti-drug antibodies N=145	p-value
CRP (mg/L)	7.5 (3.0 – 18.0)	7.0 (2.0 – 20.0)	0.75
Available (n=, %)	52 (79)	112 (77)	
Faecal calprotectin (µg/g)	425 (133 – 1440)	1004 (346 – 1905)	**0.03***
Available (n=, %)	34 (52)	71 (49)	
Last infliximab trough level (mg/L)	0 (0 – 0)	6.0 (3.9 – 8.5)	**<0.001***
Available (n=/N, %)	39/40 (98)	66/82 (80.5)	
Time since measurement (months, IQR)	0.6 (0.4 – 1.1)	1.5 (0.6 – 3.5)	
Trough, subgroup <4 months (mg/L)	0 (0 – 0)	6.3 (4.0 – 9.0)	**<0.001***
Available (n=/N, %)	38/40 (95)	54/82 (66)	
Last adalimumab trough level (mg/L)	0 (0 – 0.7)	7.7 (5.0 – 12.2)	**<0.001***
Available (n=/N, %)	23/26 (89)	48/63 (76)	
Time since measurement (months, IQR)	1.0 (0.5 – 1.3)	2.4 (1.3 – 4.8)	
Trough, subgroup <4 months (mg/L)	0 (0 – 0.7)	7.2 (4.7 – 12.2)	**<0.001***
Available (n=/N, %)	23/26 (89)	32/63 (51)	
Last trough level ≤ 1.0 mg/L (%)	53 (80)	9 (6.2)	**<0.001***
Available (n=, %)	62 (94)	114 (78.6)	
Trough <1.0mg/L, subgroup <4 months (%)	52 (79)	8 (5.5)[1]	**<0.001***
Available (n=, %)	61 (92)	86 (59)	

Supplementary Table 1. Biochemical parameters at the time of anti-TNF discontinuation (loss-of-response with versus without anti-drug antibodies) (continued)

	Loss-of-response With antidrug antibodies N=66	Loss-of-response without anti-drug antibodies N=145	p-value
Last antibody titer (AU/mL)	255 (82 – 755)	0 (0-0)	-
Available (n=, %)	58 (88)[2]	67 (46)[3]	
Time since measurement (months, IQR)	0.6 (0.4 – 1.0)	2.6 (1.0 – 6.4)	-
Titer (AU/mL), subgroup <4 months	260 (84 – 830)	0 (0-0)	
Available (n=, %)	53 (80)[2]	43 (30)	

Supplementary Table 2. Summary of incidence rates of loss-of-response with and without antibodies by treatment duration

Loss-of-response	Cumulative incidence, n (%)	Incidence rate, % per patient-year (95% confidence interval)					Trend, (p-value)[1]
Patients at risk	**N=844**	**4months – 1year N=844**	**1-2 years N=684**	**2-3 years N=477**	**3-4 years N=343**	**>4 years N=247**	
With anti-drug antibodies	**66** (7.8)	**4.9** (3.2 – 7.3)	**3.2** (1.9 – 5.0)	**2.2** (1.0 – 4.2)	**2.8** (1.2 – 5.5)	**1.2** (0.4 – 2.6)	**Decrease* (p=0.003)**
Without anti-drug antibodies	**145** (17.2)	**12.2** (9.4 – 15.7)	**7.0** (5.0 – 9.5)	**3.4** (1.9 – 5.8)	**3.9** (1.9 – 6.9)	**3.6** (2.1 – 5.7)	**Decrease* (p<0.001)**

Note that the intervals of treatment duration have different lengths, but incidence rates are reported as % per patient-year and can be compared directly. 1) Based on parametric survival modelling with Wald test for significance of decreasing/increasing versus constant hazard. *Significant at p<0.05

Supplementary Table 3. Cox regression analysis for loss-of-response (Crohn's Disease)

	Univariable HR (95% CI)	p-value	**Multivariable** HR (95% CI)	p-value
Male sex	**0.60 (0.42 – 0.85)**	**0.004***	**0.55 (0.38 – 0.78)**	**0.001***
Smoking	0.93 (0.64 – 1.35)	0.71	0.95 (0.66 – 1.39)	0.79
BMI	0.98 (0.94 – 1.01)	0.21	0.98 (0.95 – 1.02)	0.32
PSC	1.49 (0.67 – 3.34)	0.33	1.76 (0.78 – 3.95)	0.17
Age at diagnosis[2]	1.00 (0.99 – 1.02)	0.57	1.00 (0.99 – 1.02)	0.56
Age at start anti-TNF	1.00 (0.99 – 1.01)	0.63	NA	
Adalimumab (versus infliximab)	1.13 (0.81 – 1.58)	0.47	0.97 (0.68 – 1.37)	0.84
Mucosal healing[1]	0.75 (0.36 – 1.56)	0.44	0.72 (0.34 – 1.52)	0.39
Prior anti-TNF failure	1.41 (0.98 – 2.03)	0.06	1.40 (0.93 – 2.11)	0.11
Baseline immunomodulator use	0.79 (0.56 – 1.13)	0.19	0.80 (0.56 – 1.15)	0.23
Disease behavior (ref = B1)				
Stricturing/Penetrating (B2/B3)	**1.66 (1.16 – 2.36)**	**0.005***	**1.68 (1.15 – 2.46)**	**0.01***
Disease location (ref = L1, ileum)				
Colonic (L2)	0.76 (0.44 – 1.28)	0.30	0.93 (0.53 – 1.64)	0.81
Ileocolonic (L3)	0.97 (0.66 – 1.42)	0.86	1.09 (0.73 – 1.63)	0.68
Isolated L4 disease	1.74 (0.39 – 7.78)	0.47	0.89 (0.19 – 4.13)	0.89
Upper GI involvement (+L4)	**1.61 (1.03 – 2.50)**	**0.04***	1.38 (0.86 – 2.20)	0.18
Perianal disease[2]	1.15 (0.81 – 1.62)	0.43	NA	
Anti-TNF for perianal fistula	0.76 (0.47 – 1.23)	0.26	0.95 (0.58 – 1.55)	0.83

Corrected for disease duration. 1. Entered as a time changing covariate. 2 not entered in the multivariable model due to collinearity. *Significant at p<0.05

Supplementary Table 4. Cox regression analysis for loss-of-response (Ulcerative colitis).

	Univariable HR (95% CI)	p-value	**Multivariable** HR (95% CI)	p-value
Male sex	1.59 (0.93 – 2.73)	0.09	1.62 (0.88 – 2.99)	0.12
Smoking	0.75 (0.26 – 2.17)	0.60	0.68 (0.21 – 2.16)	0.51
BMI	1.01 (0.96 – 1.07)	0.57	1.01 (0.95 – 1.07)	0.82
PSC	1.91 (0.62 – 5.88)	0.26	1.40 (0.41 – 4.78)	0.60
Age at diagnosis[2]	1.01 (1.00 – 1.03)	0.11	1.01 (0.99 – 1.03)	0.30
Age at start anti-TNF	1.01 (0.99 – 1.03)	0.24	NA	
Adalimumab (versus infliximab)	1.42 (0.83 – 2.42)	0.20	1.51 (0.81 – 2.81)	0.19
Mucosal healing[1]	1.34 (0.44 – 4.12)	0.60	1.52 (0.40 – 5.80)	0.54
Prior anti-TNF failure	0.43 (0.16 – 1.17)	0.10	0.45 (0.16 – 1.29)	0.14
Baseline immunomodulator use	0.68 (0.36 – 1.27)	0.23	0.90 (0.44 – 1.83)	0.77
Extensive colitis (versus left-sided/proctitis)	0.86 (0.56 – 1.62)	0.86	0.90 (0.47 – 1.73)	0.76

Corrected for disease duration. 1) Entered as a time changing covariate. 2) not entered in the multivariable model due to collinearity.

Supplementary Table 5. Cox regression analysis for loss-of-response *with* anti-drug antibodies (All patients).

	Univariable HR (95% CI)	p-value	**Multivariable** HR (95% CI)	p-value
Male sex	0.62 (0.37 – 1.06)	0.08	**0.53 (0.31 – 0.93)**	**0.03***
UC (versus CD)	1.29 (0.72 – 2.33)	0.39	1.50 (0.79 – 2.84)	0.21
Smoking	0.95 (0.52 – 1.73)	0.85	1.03 (0.54 – 1.97)	0.88
BMI	1.01 (0.96 – 1.06)	0.67	1.01 (0.96 – 1.07)	0.60
PSC	2.49 (0.89 – 6.96)	0.08	**3.06 (1.05 – 8.91)**	**0.04***
Age at diagnosis	1.02 (1.00 – 1.03)	0.06	1.01 (1.00 – 1.03)	0.16
Age at start anti-TNF[2]	1.00 (0.99 – 1.02)	0.64	NA	
Adalimumab (versus infliximab)	0.98 (0.58 – 1.64)	0.93	0.95 (0.54 – 1.66)	0.85
Mucosal healing[1]	0.92 (0.32 – 2.66)	0.88	0.77 (0.26 – 2.29)	0.64
Prior anti-TNF failure	0.98 (0.53 – 1.83)	0.95	1.27 (0.64 – 2.53)	0.49
Baseline immunomodulator use	**0.48 (0.29 – 0.81)**	**0.006***	**0.42 (0.24 – 0.74)**	**0.002***

Corrected for disease duration. 1) Entered as a time changing covariate. 2) not entered in the multivariable model due to collinearity. *Significant at p<0.05

Supplementary Table 6. Cox regression analysis for loss-of-response *without* anti-drug antibodies (all patients).

	Univariable HR (95% CI)	p-value	**Multivariable** HR (95% CI)	p-value
Male sex	0.91 (0.66 – 1.27)	0.59	0.90 (0.64 – 1.27)	0.56
UC (versus CD)	**1.56 (1.09 – 2.25)**	**0.02***	**1.57 (1.07 – 2.30)**	**0.02***
Smoking	0.80 (0.54 – 1.19)	0.27	0.92 (0.61 – 1.40)	0.70
BMI	0.98 (0.95 – 1.02)	0.27	0.98 (0.95 – 1.02)	0.26
PSC	1.20 (0.53 – 2.73)	0.50	1.21 (0.52 – 2.83)	0.66
Age at diagnosis	1.00 (0.99 – 1.02)	0.41	NA	
Age at start anti-TNF[2]	1.01 (1.00 – 1.02)	0.23	1.01 (1.00 – 1.02)	0.28
Adalimumab (versus Infliximab)	1.22 (0.88 – 1.69)	0.24	1.23 (0.86 – 1.75)	0.26
Mucosal healing[1]	0.88 (0.42 – 1.82)	0.72	0.79 (0.37 – 1.68)	0.54
Prior anti-TNF failure	0.98 (0.53 – 1.83)	0.95	1.20 (0.78 – 1.84)	0.40
Baseline immunomodulator use	1.05 (0.73 – 1.52)	0.79	1.09 (0.74 – 1.60)	0.68

Corrected for disease duration. 1) Entered as a time changing covariate. 2) not entered in the multivariable model due to collinearity. *Significant at p<0.05

Supplementary Table 7. Biochemical parameters at the time of anti-TNF discontinuation (loss-of-response versus no loss-of-response)

	Loss-of-response	**No loss-of-response**	**p-value**
	N=211	**N=217**	
CRP (mg/L)[1]	7.0 (2.5 – 19.0)	2.0 (0 – 7.9)	**<0.001***
Available (n=, %)	164 (78)	130 (60)	
Faecal calprotectin (µg/g)[1]	857 (245 – 1661)	111 (40 – 329)	**<0.001***
Available (n=, %)	105 (50)	71 (33)	
Last IFX trough level (mg/L)	3.0 (0 – 7.0)	4.6 (1.2 – 7.9)	**0.02***
Available (n=/N, %)	105/122 (86)	95/135 (70)	
Time since measurement (months, IQR)	1.1 (0.5 – 2.0)	3.7 (1.2 – 7.8)	
IFX trough (mg/L), subgroup <4 months	2.4 (0 – 7.2)	6.0 (1.1 – 10)	**0.02***
Available (n=/N, %)	92/122 (75)	53/135 (39)	
Last ADA trough level (mg/L)	5.0 (0.7 – 9.2)	7.5 (4.3 – 12.0)	**0.01***
Available (n=/N, %)	71/89 (80)	52/82 (63)	
Time since measurement (months, IQR)	1.7 (1.0 – 3.1)	5.7 (1.8 – 15.2)	
ADA trough (mg/L), subgroup <4 months	4.0 (0.1 – 7.8)	6.7 (3.0 – 10.4)	0.08
Available (n=/N, %)	55/89 (62)	24/82 (29)	

Supplementary Table 7. Biochemical parameters at the time of anti-TNF discontinuation (loss-of-response versus no loss-of-response) (continued)

	Loss-of-response N=211	**No loss-of-response N=217**	**p-value**
Last trough level ≤ 1.0 mg/L (%)	62 (35)	26 (18)	**<0.001***
Available (n=, %)	176 (83)	147 (68)	
Trough <1.0mg/L (%), subgroup <4 months	60 (41)	16 (20.8)	**0.03***
Available (n=, %)	147 (70)	77 (35)	
Last anti-drug antibody titer (AU/mL)	255 (82 – 755)	31 (20 – 68)	**<0.001***
Available (n=, %)	58 (28)	16 (7)	**<0.001***
Time since measurement (months, IQR)	0.6 (0.4 – 1.0)	4.9 (1.9 – 8.6)	
Titer (AU/mL), subgroup <4 months	260 (84 – 830)	38 (25 – 97)	**0.02***
Available (n=, %)	53 (26)	8 (4)	**<0.001***

Continuous data presented as medians with interquartile ranges. Subgroup <4 months indicates analysis restricted to measurements conducted within 4 months prior to anti-TNF discontinuation. ADA: adalimumab. IFX: infliximab. *Significant at p<0.05.

Supplementary Table 8. Summary of incidence rates of dose escalation by treatment duration

Dose escalation	**Cumulative incidence, n (%)**	**Incidence rate, % per patient-year (95% confidence interval)**					**Trend (p-value)[1]**
		4months – 1year	**1-2 years**	**2-3 years**	**3-4 years**	**>4 years**	
At risk:	**386** (45.9) N=841	**38.0** (32.3 – 44.4) N=764	**18.7** (14.7 – 23.6) N=502	**17.9** (13.1 – 24.0) N=309	**11.9** (7.1 – 18.8) N=197	**6.8** (3.9 – 10.8) N=128	**Decrease*** (p<0.001)

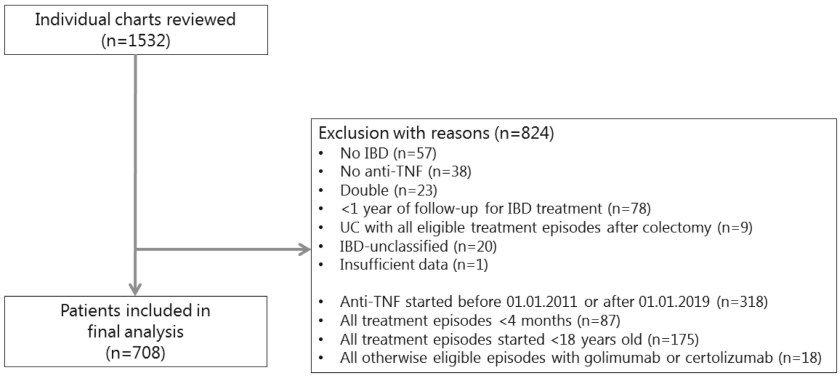
Dose escalations were unknown in 3 episodes (excluded) and occurred prior to inclusion in 77 episodes (<4 months of starting anti-TNF). Red (>20%), orange (10-20%), yellow (5-10%), green (0-5%). Note that the intervals of treatment duration have different lengths, but incidence rates are reported as % per patient-year and can be compared directly. 1) Based on parametric survival modelling with Wald test for significance of decreasing/increasing versus constant hazard. *Significant at p<0.05

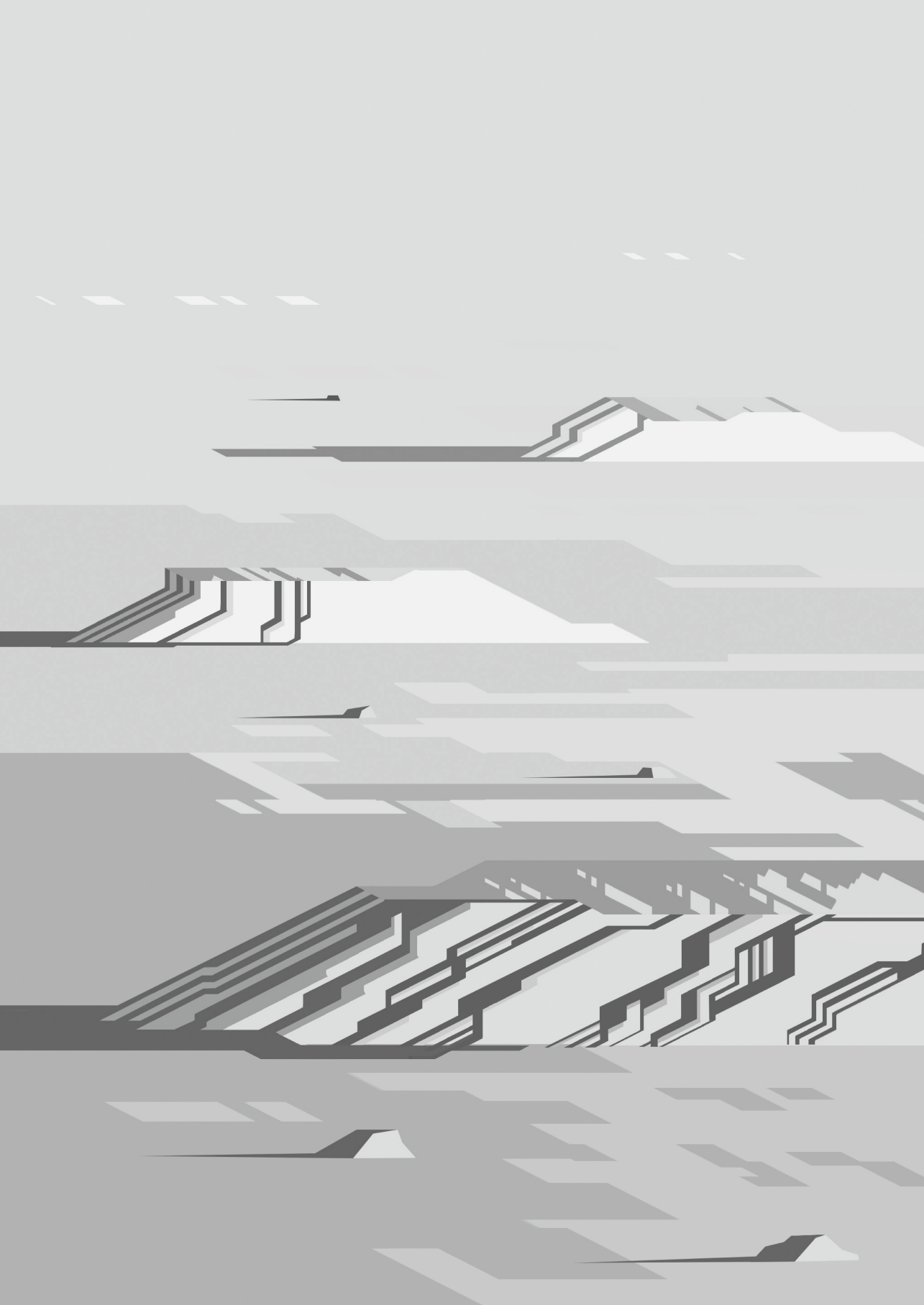
Supplementary Table 9. Trough levels and anti-drug antibodies prior to dose-escalation.

	<4 months prior to dose escalation (N=310)
Trough level and/or anti-drug antibodies measured, n= (%)	222 (71.6)
Infliximab trough level, mg/L Available (n=, %)	1.6 (0.6 – 2.6) 132/195 (67.7)
Anti-infliximab antibody titer, AU/mL Available (n=, %)	36 (20-58) 17/195 (8.7)
Adalimumab trough level, mg/L Available (n=, %)	3.8 (1.8 – 5.1) 83/115 (72.2)
Anti-adalimumab antibody titer, AU/mL Available (n=, %)	27 (15-83) 19/115 (16.5)

Continuous parameters presented as medians with interquartile ranges.

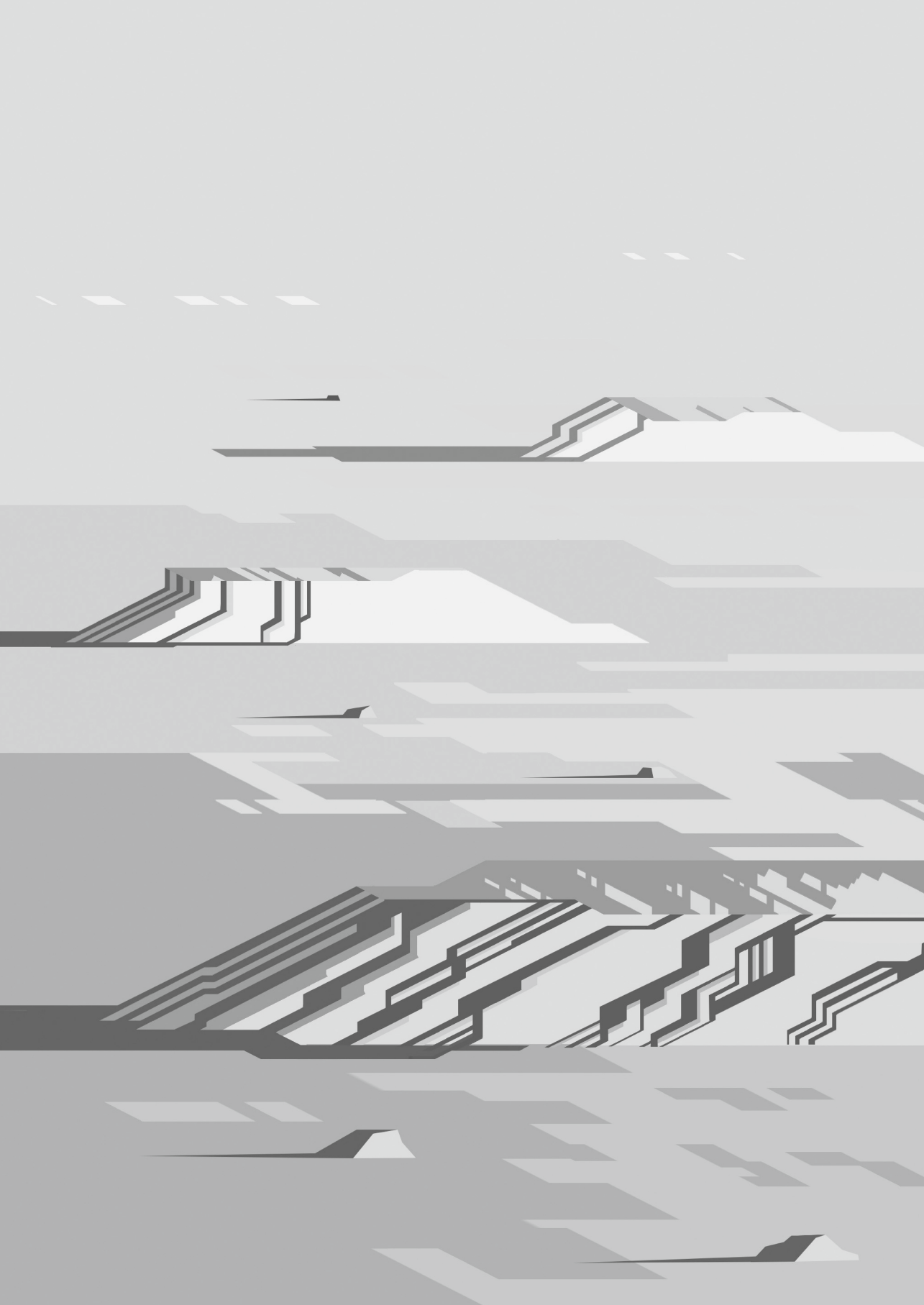
Supplementary Figure 1. Flow diagram of the selection process.





SECTION II

Colitis-associated dysplasia and cancer



Chapter 6

Surveillance and management of colorectal dysplasia and cancer in inflammatory bowel disease: current practice and future perspectives

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Eur J Intern Med. 2021 Nov;93:35-41.

Abstract

Patients with inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer (CRC). Current guidelines recommend frequent surveillance colonoscopies for patients with at least left-sided ulcerative colitis, or Crohn's disease involving more than 30% of the colon. Surveillance allows for early detection and treatment of colorectal dysplasia and cancer. The first colonoscopy should be performed 8 to 10 years after onset of disease symptoms. European and British guidelines employ a risk-stratification algorithm that assigns patients to surveillance intervals of one, three or five years, whereas American guidelines recommend to perform surveillance every 1 to 3 years based on the (combined) presence of risk factors. Patients with concomitant primary sclerosing cholangitis are at an additionally increased risk, and should undergo annual surveillance starting immediately after the diagnosis. The current practice of surveillance is based on limited evidence, is resource intensive and cannot preclude the occurrence of interval carcinomas. Fortunately, advances in endoscopic techniques for mucosal visualisation, along with better control of inflammation, have resulted in a declining incidence of CRC in patients with IBD. Furthermore, advanced endoscopic resection techniques can be expected to result in a shift from surgical to endoscopic management of dysplastic lesions. In this review, we provide an up-to-date overview of colitis-associated CRC pathophysiology, epidemiology, surveillance practices, and management of dysplasia.

Keywords
Colitis-associated neoplasms; Review; Ulcerative colitis; Crohn's disease

Introduction

Almost a century ago, Crohn and Rosenberg described the first case of ulcerative colitis (UC) complicated by colorectal carcinoma (CRC).[1] Nowadays, it is widely recognised that patients with colonic inflammatory bowel disease (IBD), including UC and Crohn's disease (CD), are at increased risk of CRC and therefore these patients are enrolled in surveillance programs.[2-8] Endoscopic surveillance aims to detect and remove precursor lesions or early-stage CRC, and has been linked to a decreased risk of CRC and corresponding mortality based on retrospective data.[9]

The development of novel endoscopic technologies has had an enormous impact on endoscopy practices. High-definition endoscopes allow for detailed visualisation of the colonic mucosa, and novel resection techniques enable endoscopic treatment of lesions that previously had to be removed surgically.[10] This technological progress, along with the expanding therapeutic armamentarium to control inflammation,[11, 12] likely explains why the incidence of colitis-associated CRC has declined over time.[3]

In the light of these developments, this review aims to provide an up-to-date overview on the pathophysiology, epidemiology, surveillance strategies and management of colitis-associated dysplasia and cancer. Furthermore, we will highlight several areas of interest for further research.

Pathophysiology

According to the widely accepted *adenoma-carcinoma sequence* paradigm, most cases of sporadic CRC develop from adenomatous polyps over a long period of time.[13] Colitis-associated CRC is thought to develop through several stages of precursor lesions as well, from inflamed but non-dysplastic epithelium to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and finally CRC.[14, 15] Here, chronic inflammation is thought to be the main driver of tumourigenesis.[14] Indeed, endoscopic or histologic inflammation, and extensive disease are well-known independent risk factors for colorectal dysplasia and cancer in IBD.[16, 17]

A unique feature of the pathogenesis of colitis-associated CRC is that chronic inflammation leads to a 'field defect' of damaged DNA in colonic epithelial cells, rather than unifocal aberrant clones.[14] Small genomic alterations may be present throughout the (entire) colon affected by colitis in normally appearing, non-dysplastic mucosa.[18] From these areas, dysplastic lesions arise, which are usually endoscopically visible, using current high-definition endoscopes.[19] This field defect or 'field cancerisation' explains why dysplasia in IBD is often multifocal.[19-21]

At a genetic level, in line with sporadic CRC, most colitis-associated CRCs develop through the chromosomal instability pathway as opposed to the microsatellite instability pathway (i.e. malfunctioning of DNA mismatch repair genes, involved in Lynch syndrome).[14, 22, 23] The chromosomal instability pathway manifests by copy number alterations of chromosomes or parts of chromosomes (i.e. aneuploidy) and includes changes to the APC, TP53 and K-RAS genes,[14] among others. It is thought that these changes occur in a different sequence in colitis-associated versus sporadic CRC. For example, APC mutations are more frequent in precursors lesions of sporadic CRC (sporadic adenomas),[23] while colitis-associated precursor lesions usually harbour TP53 mutations.[24, 25] This differential sequence may explain why colitis-associated dysplasia can be morphologically distinct from sporadic adenomas, as it is often non-polypoid.[20, 21]

The gut microbiome differs between IBD patients and healthy individuals,[26] and this has recently been linked to the increased CRC risk in patients with IBD.[27] A specific strain of *Escherichia Coli* (polyketide non-ribosomal peptide synthase operon [pks] positive strain) has a twofold higher prevalence in IBD patients as compared to healthy individuals.[27] This pks-positive *Escherichia Coli* strain produces a toxin (colibactin) that damages DNA and induces a specific signature of mutations (including mutations in the APC gene and genes involved in the TP53-axis, among others) in intestinal organoids.[28 29] These preliminary findings might, in the future, lead to new targets for preventive strategies.

Finally, it should be noted that patients with IBD may also develop sporadic adenomas. Since the prognosis differs for colitis-associated dysplasia versus sporadic adenoma in IBD patients,[30] various efforts have been made to identify endoscopic or histopathological characteristics that can help making this distinction. Currently, the distinction is based on lesion morphology, presence of multifocal dysplasia, and whether the lesion is located in an area previously affected by inflammation.

Epidemiology

Excess risk of CRC in patients with IBD

Patients with IBD are at an 1.4 to 2.2 fold increased risk of CRC compared with the general population.[3, 31-33] Furthermore, CRC-related survival is lower among patients with IBD, even after adjustment for tumour stage at diagnosis.[32-34] Thus, both a higher incidence of CRC as well as worse clinical outcomes of colitis-associated CRC contribute to an overall increased rate of CRC-related mortality in patients with IBD.[32, 33]

The incidence of IBD-CRC is considerably higher in hospital-based studies as compared to population-based studies (1.7-3.0 per 1,000 patient-years and 0.8-1.3 per 1,000 patient-years, respectively).[31-33, 35-37] Cohort studies of patients undergoing surveillance report the highest IBD-CRC incidences (3.1-4.7 per 1,000 patient-years).[30, 38] Beaugerie's landmark study showed that IBD patients with a disease duration of more than ten years and involvement

of more than half of the colonic mucosa are at a 5.2-fold (UC) and 9.0-fold (CD) increased risk of CRC compared with the general population. In contrast, patients in whom such long-standing, extensive colitis was not present had a similar CRC risk as non-IBD controls.[31]

Interestingly, the excess risk of CRC in patients with IBD has been found to decline over time in most regions where this has been examined,[3, 32] but not all.[3, 35] This decline may be explained by advances in surveillance techniques and improved management of inflammation.[2, 3] Of note, results from the longest-running surveillance cohort in patients with UC initially indicated a decreasing CRC incidence, but subsequently reported an increase in early CRC. The authors attributed this phenomenon to a shift from managing dysplasia surgically (i.e. colectomy) to endoscopic resection.[30] Reassuringly, the incidence of advanced CRC had continued to decline in the last decade.

Risk factors

Risk factors for HGD and CRC combined ('advanced colorectal neoplasia', a commonly used composite endpoint in studies) in patients with IBD include extensive colonic disease, presence of post-inflammatory polyps, colonic strictures and severity of histologic inflammation.[17] These factors are all closely related to the cumulative inflammatory burden,[16] and underpin the central role of inflammation in the pathogenesis of colitis-associated CRC. The main challenge therefore, is to create a pragmatic score for cumulative inflammation (either based on histology or endoscopy), that can be readily implemented in routine practice.

In addition to the abovementioned phenotypic features related to inflammation, primary sclerosing cholangitis (PSC) is a very strong risk factor for HGD and CRC in patients with IBD as well.[17, 39] PSC is a chronic progressive cholestatic liver disease leading to biliary inflammation and fibrosis,[39] that is exceedingly rare in the general population, but is present in 3-5% of patients with IBD (mainly UC patients).[30, 40] Similar to sporadic CRC, older age, a positive family history of CRC and male sex also increase the risk of colitis-associated HGD and CRC.[17] Moreover, IBD patients with prior indefinite dysplasia or LGD are also at increased risk of HGD and CRC.[17] The latter may be explained by various factors, including local recurrence (inadequate resections), missed synchronous lesions, or the aforementioned "field defect" of damaged DNA that extends beyond the dysplastic lesion. Notably, aneuploidy in biopsies from normally appearing mucosa may indicate a field defect and is indeed associated with a more than fivefold increased risk of HGD or CRC.[17]

Surveillance

Surveillance strategies

Leading guidelines recommend to perform surveillance in patients with colonic IBD. A first surveillance colonoscopy should be scheduled in all patients with colonic IBD either 8 to 10 years after onset of symptoms.[4-8] Continued surveillance is recommended if the

colonic involvement exceeds proctitis (UC) or is more than 30% (CD). European and British guidelines stratify patients in one of three risk categories (high, intermediate, or low risk group) with surveillance intervals ranging from annually to every five years (Figure 1).[4, 5] American guidelines recommend to perform surveillance every 1 to 3 years and to consider the (combined) presence of risk factors when determining the next surveillance interval.[6-8] Importantly, IBD patients with concomitant PSC are a distinct category. For these patients, all guidelines recommend annual surveillance, starting immediately after the diagnosis because of the strongly increased CRC risk in patients with PSC.[4-8, 17]

The (cost)effectiveness of the algorithms recommended in current guidelines has never been investigated prospectively and the available evidence is insufficient to objectively define optimal, individualised surveillance intervals. As a result, current surveillance regimens undoubtedly lead to overutilisation of health care resources, as most IBD patients will never develop CRC. This is underscored by a previous cost-effectiveness modelling study that found a risk-stratification approach for surveillance to be more cost-effective than annual or biannual surveillance.[41] Meanwhile, 30% of CRC cases in IBD are missed during surveillance and can therefore be classified as interval carcinomas.[42] Furthermore, half of the CRCs diagnosed in patients with IBD who underwent a colonoscopy in the past five years, can be attributed to a previously missed lesion, despite adequate procedural quality measures.[37] These findings highlight the need for an evidence-based systematic approach to identify patients with IBD in whom surveillance is indicated,[35, 43, 44] as well as the importance of optimising surveillance techniques to reduce the risk of missed lesions.

Surveillance technique

Colonoscopy is the gold standard for CRC surveillance in IBD patients. Optimal bowel preparation and disease remission are absolute requirements for adequate surveillance.[42, 45] Present guidelines recommend to perform surveillance colonoscopies employing chromoendoscopy.[4-6, 8, 46] Chromoendoscopy creates enhanced images by directly spraying dye on the colonic mucosa during endoscopy (Figure 2). Lichtenstein et. al. published an educational video that illustrates this technique.[47] Downsides of chromoendoscopy are that this technique prolongs procedure time, requires additional training, and may be perceived as impractical by endoscopists.[48] It can be questioned whether the advent of high definition (HD) endoscopy has made chromoendoscopy redundant. Previous meta-analyses including only randomised controlled trials (RCT) reported similar dysplasia detection rates with and without chromoendoscopy in patients with IBD.[48-50] In contrast, superiority of surveillance using chromoendoscopy was reported in a recent well-conducted RCT from Sweden (Supplementary Table 1 provides summary data of these RCTs).[51] Nowadays, most guidelines still recommend chromoendoscopy, but also state that white light endoscopy using HD endoscopes is a good alternative.

Figure 1. Surveillance strategy of the European Crohn's and Colitis Organisation (ECCO)[4]

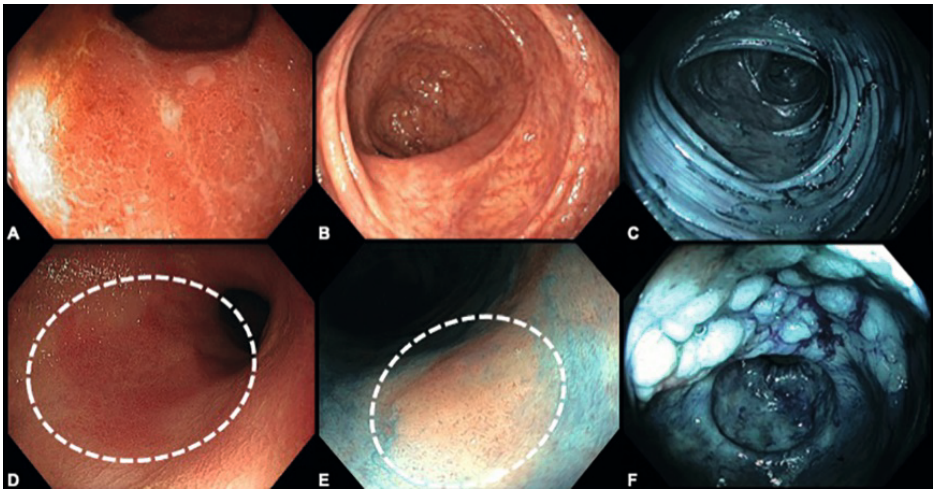
***** Presence of inflammation is based on endoscopic or histologic inflammation. CRC=colorectal cancer, PSC=primary sclerosing cholangitis.

The role of random biopsies, four biopsies every ten centimetres, in surveillance colonoscopies, using HD endoscopes, has also become unclear.[46] The rationale for random biopsies is that they may detect dysplastic lesions that cannot be identified endoscopically. As with chromoendoscopy, taking random biopsies prolongs procedure time and additionally adds costs of histopathologic evaluation. In this era of HD endoscopes, the neoplastic yield of *only* random biopsies in IBD patients in the setting of surveillance is quite low, 1.2-3.0% per-colonoscopy and 0.09-0.2% per biopsy.[51, 52] Non-inferiority in neoplasia detection was reported for surveillance with *only* targeted biopsies versus target and random biopsies in a RCT study, although no data on long-term outcomes were reported.[53] The yield of random biopsies is higher in patients with concomitant PSC (3.7% per-colonoscopy and 0.3% per biopsy),[51, 52, 54, 55] prior dysplasia, or a tubular colon.[52] The added value of random biopsies

in these high-risk patients should be balanced against additional costs and potential risks, e.g. of surgical procedures. In a retrospective cohort study including 71 UC patients with concomitant PSC, the diagnosis of invisible (without visible) dysplasia in random biopsies, detected in eight patients, impacted clinical outcomes.[55] As high-risk patients already receive frequent surveillance, the additional impact of detecting invisible dysplasia might be overestimated, however.

Thus, to define the optimal surveillance technique when using HD endoscopes, more research is needed to determine the (cost)effectiveness of HD-endoscopy with versus without chromoendoscopy and/or random biopsies.

Figure 2. Examples of endoscopy images



A: Moderate disease (the colonic mucosa shows marked erythema, absent vascular pattern, and erosions); B: Normal colonic mucosa (the colonic mucosa shows a normal vascular pattern, no erythema); C: Normal colonic mucosa (chromoendoscopy); D: Flat colitis-associated neoplasia; E: Colitis-associated neoplasia (methylene blue is rapidly absorbed by normal mucosa, but the absorption in neoplastic mucosa is impaired); F: Large colitis-associated neoplastic lesion (chromoendoscopy).

Unmet needs

To further improve surveillance strategies in IBD patients, we believe a novel prediction model is warranted. Such a model should be easy to implement in clinical practice, while accounting for the presence of multiple risk factors and their effect sizes. The potential place of biomarkers (e.g. aneuploidy) as prognostic factors should also be evaluated. Additionally, exit strategies for surveillance should be explored. One study indicated that after two consecutive surveillance colonoscopies without abnormalities (defined as no post-inflammatory polyps, strictures, dysplasia or CRC, or endoscopic disease activity),

the subsequent risk of HGD or CRC is negligible.[56] Discontinuation of surveillance in patients at lowest risk of CRC, as is recommended in the Dutch guideline,[57] will reduce the burden for patients and the healthcare system considerably. It is presently not clear what strategy should be adopted in IBD patients in whom surveillance is discontinued. Enrolment in a nationwide, faecal occult blood test (FOBT)-based, screening program seems practical, but the accuracy of FOBT is diminished by mucosal inflammation,[58] rendering this type of surveillance less effective.

Management of dysplasia

Until recently, guidelines recommended to perform a proctocolectomy in case of colorectal dysplasia in patients with IBD, based on a high perceived risk of synchronous dysplasia in this setting. Nowadays, treatment of these lesions is increasingly moving towards endoscopic options, where interventions are tailored based on patient and lesion characteristics.

It must be emphasized that a diagnosis of colorectal dysplasia or cancer in IBD patients should be confirmed by a second pathologist with expertise in this field.[4, 6, 8, 46, 59] This recommendation is based on the high level of interobserver variability (especially for LGD and indefinite dysplasia)[60, 61] which, at least partly, can be attributed to the presence of histologic inflammation.[61, 62]

First, a distinction between endoscopically visible and invisible dysplasia has to be made.[46] If invisible dysplasia is detected in random biopsies, present guidelines advise to consider strict continued surveillance, reassessment by an IBD expert, or surgical treatment.[46] This choice is based on the grade of dysplasia, presence of unifocal versus multifocal invisible dysplasia, synchronous visible dysplasia as well as patient characteristics (e.g. age, comorbidity) and preferences. In case of a visible lesion, the first step is to determine whether the lesion can be resected endoscopically, and if so, which technique should be used. This depends on lesion size, shape, site (colitis-associated area or not), surface, and surrounding area (together known as Five "s" characteristics), risk of invasion (amongst others based on Five "s" criteria) and endoscopic accessibility.[46, 63] Small polypoid and non-polypoid lesions can be removed with a simple endoscopic resection technique using snares.[8] For larger lesions endoscopic mucosal resection (EMR) is used, a technique that involves lifting of the lesion from the muscularis propria using a submucosal injection with saline to permit safe removal of the lesion with a snare. Endoscopic submucosal dissection (ESD) should be considered for large (>20mm) lesions, especially if these are non-polypoid or display high-risk features. In ESD the lesion is lifted from the muscularis propria, followed by dissection of the lesion from deeper layers using an endo-knife. ESD has the advantage of high *en bloc* resection rates (even in case of submucosal fibrosis which is frequently encountered in colitis-associated lesions), high numbers of radical (R0) resections at histopathologic examination, and is associated with low risk of adverse events such as bleeding or perforation.[10] Furthermore, previous studies on ESD in IBD patients report low local recurrence rates and small numbers

of metachronous lesions, although these studies have relatively short follow-up periods and small sample sizes.[10] Table 1 summarises the main advantages and disadvantages of endoscopic resections using an EMR or ESD technique. Educational videos on these techniques were previously published.[47, 64, 65] Importantly, when a lesion is successfully resected endoscopically, strict endoscopic follow-up is needed.[46]

Surgery is the treatment of choice for endoscopically non-resectable lesions, invisible dysplasia (especially in case of HGD), and/or 'high risk' colons.[46, 66] A total proctocolectomy is recommended in case of HGD or CRC, in order to also reduce the future risk of dysplasia and cancer.[8, 67] After a total proctocolectomy, a pouch (reservoir) can be constructed from the terminal ileum with an anastomosis to the anal canal, as an alternative to a permanent ileostomy. Guidelines state that in patients diagnosed with LGD not involving the rectum, or in presence of comorbidities, a subtotal colectomy with ileorectal anastomosis or ileostomy, or segment resection can be considered.[67] Importantly, after a subtotal colectomy (or even segmental colonic resection), the remaining colonic mucosa remains at risk for dysplasia and cancer.[68] Also, colectomy is associated with a 1% risk of perioperative mortality, risk of long-term complications (e.g. faecal incontinence or leakage, ileus or small bowel obstruction, fistulae) and reduced quality of life.[69, 70]

To further improve the management of dysplasia, future studies should examine the long-term oncological safety and efficacy of both advanced endoscopic resection techniques and limited surgical resections (segment resections or subtotal colectomy for endoscopically non-resectable lesions).

Table 1. Advantages and disadvantages of EMR and ESD

	Endoscopic mucosal resection (EMR)	**Endoscopic submucosal dissection (ESD)**
Resection plane	+ Submucosa	+ Submucosa
Suitable lesions	- Smaller polypoid and non-polypoid lesions	+ Large (>20mm), high-risk lesions and non-polypoid lesions
Procedure time	+ Relatively short	- Long
Learning curve	+ Relatively short	- Relatively long
Adverse events	+ Low	+/- Low, but higher than EMR
Histopathological examination	- Difficult, due to frequent piecemeal resections[1]	+ Good, due to high rate of *en bloc* resections
Radical (R0) resections rate	- Relatively low	+ High

EMR=Endoscopic mucosal resection, ESD=Endoscopic submucosal dissection.1)i.e. fragmented resections, especially when treating larger lesions with EMR.

Chemoprevention

In theory, every therapeutic agent that effectively induces and maintains remission in IBD will decrease the risk of CRC, because inflammation is the main driver behind tumourigenesis in colitis-associated CRC. However, the role of maintenance therapy in the prevention of colitis-associated dysplasia and cancer is currently unclear. Most evidence for chemoprevention is based on retrospective studies with varying definitions of medication use. Moreover, most studies did not adjust for (cumulative) inflammation and should therefore be interpreted with caution.

Previous meta-analyses report a negative association of 5-aminosalicylic acid (5-ASA) use and development of dysplasia and CRC in IBD (mostly UC patients).[17, 71, 72] This finding might be explained by anti-inflammatory effects, direct chemoprotective properties of 5-ASA at a molecular level, or a milder phenotype of patients on 5-ASA (mono)therapy.[73] The protective effect of 5-ASA on the risk of dysplasia and CRC seems to be dose-related, which additionally supports its role in this setting.[71]

Thiopurine use has also been found to prevent the development of dysplasia and CRC.[74-76] A recent meta-analysis did not show a protective effect of TNF-alpha inhibitors on HGD and CRC. Of note, TNF-alpha inhibitors are usually prescribed in patients with more severe disease, which might have confounded the results considerably.[74] Theoretically, both thiopurines and TNF-alpha inhibitors could either decrease the risk of CRC by reducing colonic inflammation, but also increase the risk of CRC through their immunosuppressive effects.

In patients with IBD and concomitant PSC, a meta-analysis reported no overall reduction in the risk of dysplasia and CRC in patients using ursodeoxycholic acid (UDCA). However, the risk of dysplasia and CRC was lower in a subgroup of patients using low-dose UDCA (8-15 mg/kg) (OR 0.19, 95% CI 0.08-0.49).[77] In contrast, the use of high-dose UDCA (15-30 mg/kg) is reportedly associated with a trend towards an increased risk of colorectal dysplasia or cancer in pooled analysis (OR 2.03, 95% CI 0.53-7.73),[77] and other adverse outcomes such as mortality and liver transplantation.[78, 79] Current British guidelines recommend against the use of ursodeoxycholic acid for the sole purpose of preventing CRC.[80]

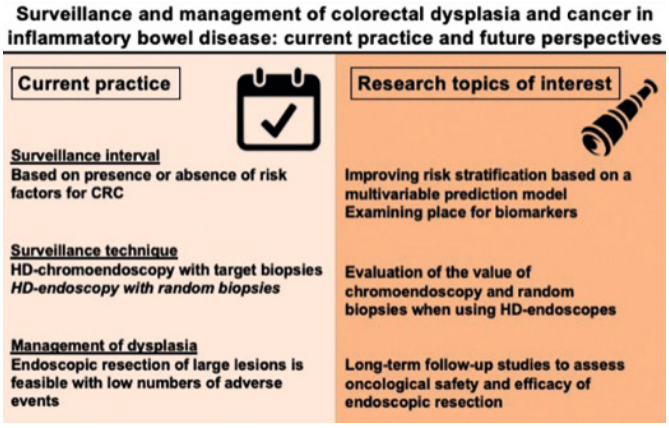
Overall, guidelines are not consistent with respect to prescribing specific drugs solely for chemopreventive purposes in patients not requiring maintenance therapy.

Conclusion

In conclusion, the risk of CRC in patients with colonic IBD is increased, especially among those with a high (prior) inflammatory burden, concomitant PSC, or a history of dysplasia. The current practice of colonoscopic surveillance aims to detect and remove precursor lesions of CRC and thereby mitigate the excess CRC risk in patients with IBD. Some studies, but not all, indicate that the CRC risk in IBD has declined over the last decades, which has been ascribed to the wide implementation of surveillance colonoscopies, advanced endoscopic techniques for mucosal visualisation and lesion resection, and improved management of inflammation.

The mainstay in the management of these patients remains colonoscopic surveillance. This resource-intensive procedure imposes a significant burden on patients, while interval CRCs still occur too frequently. In this review, we have highlighted several areas of interest for future research (Figure 3). More research is needed to develop a prediction model to determine individualised surveillance intervals, to assess the necessity of taking random biopsies and/or using chromoendoscopy with modern HD endoscopes, and to establish the long-term efficacy and safety of advanced resection techniques such as ESD in patients with IBD.

Figure 3. Current practice and future perspectives



CRC=colorectal cancer, HD=high-definition.

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Supplementary Table 1. Summary of RCTs comparing HD-chromoendoscopy versus HD-white light endoscopy in IBD

Author, year	Country	Study design	Study period	Number of patients	Study/ procedure details	CE: Number of patients with ≥1 macroscopic dysplastic lesions	WLE: Number of patients with ≥1 macroscopic dysplastic lesions	Intention-to-treat analysis (p-value)	Per protocol analysis (p-value)
Alexandersson et. al., 2020[1]	Sweden	RCT, single-centre	2011-2016	305	CE *and* WLE including 32 random biopsies.	17/152	7/153	**0.032**	**0.027**
Iacucci et. al., 2018[2]	Canada	RCT, single-centre, non-inferiority	2014-2016	270	No random biopsies. *Note: Non-inferiority margin powered for comparing CE versus virtual CE.*	22/90	23/90	0.91	Not reported.
Mohammed et. al., 2015[3] *Abstract only*	United Kingdom	RCT, single-centre	Not reported.	103	No details on random biopsies.	11/50	5/53	**0.04**	Not reported.

Supplementary Table 1: Summary of RCTs comparing HD-chromoendoscopy versus HD-white light endoscopy in IBD (continued)

Author, year	Country	Study design	Study period	Number of patients	Study/ procedure details	CE: Number of patients with ≥1 macroscopic dysplastic lesions	WLE: Number of patients with ≥1 macroscopic dysplastic lesions	Intention-to-treat analysis (p-value)	Per protocol analysis (p-value)
Yang et. al., 2019[4]	South Korea	RCT, multi-centre	2013-2015	210	WLE group: 4-quadrant random biopsies every 10cm.	13/108*	21/102*	0.093	Not reported.

CE=chromoendoscopy; RCT=randomised controlled trial; WLE=white light endoscopy
*Defined as all CRN detected in this study. Yang et. al. also performed a separate analysis on colitis-associated dysplasia reporting no difference between HD-chromoendoscopy with target biopsies versus HD-WLE with random biopsies (p 0.749)

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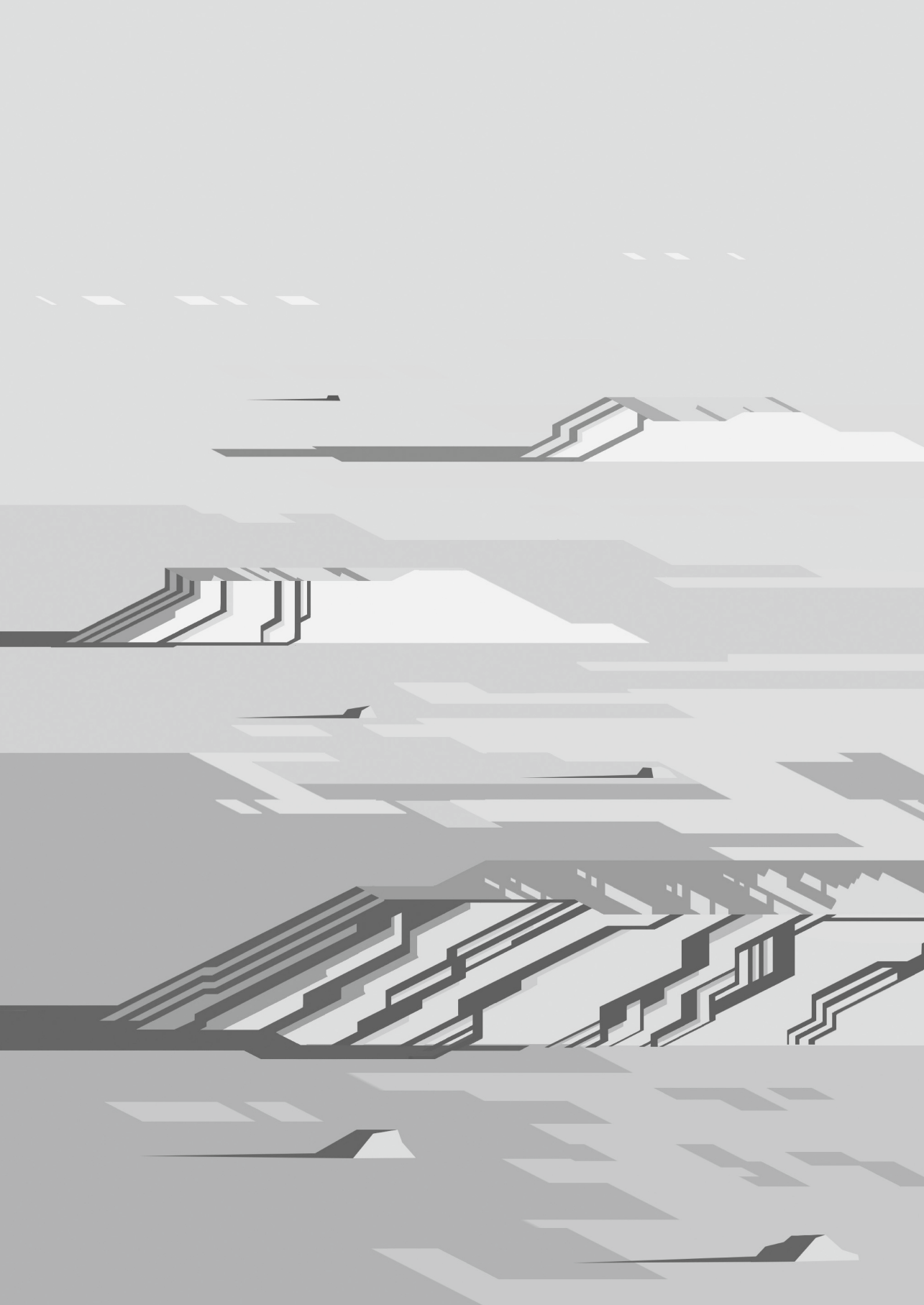

Chapter 7

No Association Between Pseudopolyps and Colorectal Neoplasia in Patients With Inflammatory Bowel Diseases

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Gastroenterology. 2019 Apr;156(5):1333-1344.

Abstract

Background & Aims

Patients with inflammatory bowel diseases (IBD) who have post-inflammatory polyps (PIPs) have an increased risk of colorectal neoplasia (CRN). European guidelines propose that patients with PIPs receive more frequent surveillance colonoscopies, despite limited evidence of this increased risk. We aimed to define the risk of CRN and colectomy in patients with IBD and PIPs.

Methods

We conducted a multicenter retrospective cohort study of patients with IBD who underwent colonoscopic surveillance for CRN, from January 1997 through January 2017, at 5 academic hospitals and 2 large non-academic hospitals in New York or the Netherlands. Eligible patients had confirmed colonic disease with duration of 8 years or more (or any duration, if they also have primary sclerosing cholangitis) and no prior history of advanced CRN (high-grade dysplasia or colorectal cancer) or colectomy. The primary outcome was occurrence of advanced CRN according to PIP status; secondary outcomes were occurrence of CRN (inclusive of low-grade dysplasia) and colectomy.

Results

Among 1582 eligible patients, 462 patients (29.2%) had PIPs. PIPs were associated with more severe inflammation (adjusted odds ratio [aOR], 1.32; 95% CI, 1.13–1.55), greater disease extent (aOR 1.92; 95% CI, 1.34–2.74), and lower likelihood of primary sclerosing cholangitis (aOR 0.38; 95% CI, 0.26–0.55). During a median follow-up period of 4.8 years, the time until development of advanced CRN did not differ significantly between patients with vs without PIPs. PIPs did not independently increase risk of advanced CRN (adjusted hazard ratio, 1.17; 95% CI, 0.59–2.31). The colectomy rate was significantly higher in patients with PIPs (P=0.01).

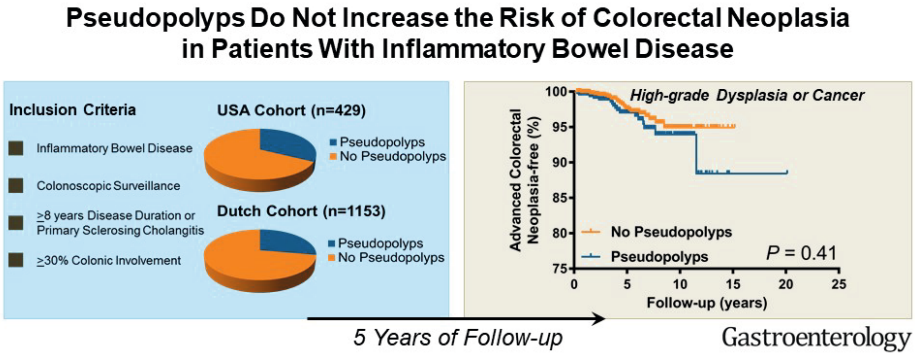
Conclusions

In a retrospective analysis of data from 2 large independent surveillance cohorts, PIPs were associated with greater severity and extent of colon inflammation and higher rates of colectomy, but were not associated with development of any degree of CRN. Therefore, intervals for surveillance should not be shortened solely based on the presence of PIPs.

Keywords

PSC; Ulcerative Colitis; Crohn's Colitis; Crohn's Disease; Quality Improvement; Endoscopy

Graphical Abstract



Introduction

Patients with longstanding inflammatory bowel disease (IBD) colitis are at increased risk of developing colorectal dysplasia and colorectal cancer (CRC).[1,2] Current guidelines recommend performing surveillance colonoscopies at regular intervals to screen for colorectal neoplasia (CRN, dysplasia or carcinoma).[3–6] Leading European guidelines stratify patients with IBD colitis into groups with low, intermediate or high-risk of CRC based on several risk factors, including the presence of post-inflammatory polyps (PIPs).[3,5,6] Commonly referred to as "pseudopolyps", PIPs are encountered in 20-45% of patients with IBD and colonic involvement.[7–10] Older case-control studies reported a 1.9- to 2.5-fold increased risk of CRC in patients with PIPs.[8,9,11] More recently, however, in a large retrospective cohort study of patients with ulcerative colitis (UC) undergoing CRN surveillance, PIPs did not independently predict CRN or predict progression from low-grade dysplasia (LGD) to advanced CRN (ACRN; defined as high-grade dysplasia (HGD) or CRC).[10,12]

Theoretically, the risk of CRN could be increased in patients with PIPs if their presence indicates prior severe inflammation. Alternatively, PIPs may obscure otherwise visible and resectable dysplastic lesions during surveillance. Direct malignant transformation of PIPs is generally considered unlikely.[13] Regardless of the mechanism, there is a gap in the literature as to whether PIPs are independent predictors of ACRN. Clarifying this risk has far-reaching implications with respect to the burden of surveillance colonoscopies in patients with IBD and PIPs. If possible, safe lengthening of surveillance intervals would impact quality of life and promote cost containment and resource stewardship. Using a large multicenter cohort of patients with confirmed colonic IBD undergoing colonoscopic surveillance, we primarily aimed to determine whether PIPs are associated with increased risk of ACRN, and secondarily with CRN or colectomy. We also aimed to delineate predisposing or protective factors for PIPs and to define the prevalence of CRN in biopsied PIPs.

Methods

Study design and population

This retrospective cohort study identified patients with confirmed colitis undergoing colonoscopic surveillance for CRN between January 1997- January 2017 from two large IBD cohorts: the Mount Sinai Hospital (MSH, New York, USA) cohort and a Dutch cohort coordinated by the Utrecht University Medical Center (UMCU, Utrecht, The Netherlands), comprising 5 academic hospitals and 2 large non-academic hospitals. The search strategy has been described in detail previously.[14] Inclusion criteria were: 1) diagnosis of IBD (UC, Crohn's disease (CD), IBD-unclassified (IBD-U)); 2) confirmed colonic disease by endoscopy and histology of at least 8 years, or of any duration if concomitant primary sclerosing cholangitis (PSC; confirmed by ERCP, MRCP, or liver biopsy); 3) enrollment in a dysplasia surveillance program; 4) $\geq$ 2 surveillance colonoscopies with available colonoscopy and pathology reports, or $\geq$ 1 surveillance colonoscopy if interval

ACRN was diagnosed on pathology obtained by another method; 5) at least left-sided disease extent (UC), involvement of >30% of the colonic surface (CD or IBD-U), or any extent if concomitant PSC; and, after meeting these inclusion criteria, 6) no history of ACRN or colectomy prior to (or within the three months following) the first surveillance colonoscopy within the predefined study period (i.e. "index colonoscopy").

Data collection

The following baseline and clinical data were collected from the electronic health record (EHR) documentation using the same data collection format and definitions for both cohorts: date of birth, sex, age at IBD diagnosis, IBD type (UC, CD, or IBD-U), family history of CRC, diagnosis of PSC (confirmed by histology or endoscopic/radiologic cholangiography) and prior history of colonic dysplasia (defined as indefinite for dysplasia (IND) or LGD at or before the index colonoscopy). Maximum extent of colonic disease was determined based on prior history as documented in the EHR and maximal disease extent during colonoscopic surveillance according to either endoscopic and/or histologic findings. Any documented exposure to medication was collected before and during follow-up, including 5-aminosalicylates (5-ASA), immunomodulators (azathioprine or 6-mercaptopurine), methotrexate and biologicals (including infliximab, adalimumab, certolizumab, golimumab, ustekinumab, natalizumab and vedolizumab). Surveillance procedures were defined as colonoscopies in which either segmental random biopsies or chromoendoscopy were employed. Data from these procedures were collected from colonoscopy and pathology reports. In addition, data from any procedure (e.g. colectomy) leading to a diagnosis of ACRN were recorded. Colonoscopies that did not meet these criteria were excluded. Endoscopic inflammation (1 - Normal/inactive; 2 – Mild; 3 – Moderate; 4 – Severe) and histologic inflammation (1- Normal; 2 – Inactive; 3 - Mild; 4 - Moderate; 5 – Severe) were scored per segment. A mean inflammation score was calculated by averaging the scores of the most severely inflamed segment of all recorded surveillance colonoscopies.

For each endoscopic (or surgical) procedure, the following data were collected: date of procedure, presence of PIPs, quality of bowel preparation (adequate [excellent or good] or inadequate [fair or poor]), extent of intubation and endoscopic/histologic inflammation. Quality measures were reported relative to the number of surveillance procedures performed during follow-up (i.e. percentage of procedures with adequate bowel preparation or cecal intubation). For the USA cohort only, if the endoscopy report described PIPs as "many", "limiting visibility" or "fields" patients were subclassified as having "many PIPs". In the absence of these descriptors, patients were subclassified as having "few PIPs". Furthermore, colonic location of PIPs, number of PIPs biopsied (including any lesion that was reported to be a PIP in the endoscopy or pathology report), and presence and grade of dysplasia in aforementioned lesions were extracted. These data were not available in the Dutch cohort.

Histologic diagnosis and highest grade of CRN (defined as LGD, HGD, CRC) or IND were recorded per segment. At all participating institutions, specimens with suspected CRN are routinely reviewed by at least two pathologists. No samples were re-reviewed and no alterations to the finalized reports were made for the purposes of this study.

Colectomy was defined as either subtotal colectomy or total proctocolectomy. Colectomy date and indication (medically refractory disease (MRD), stricture, dysplasia (CRN of any degree, suspected or confirmed) or multiple (combination of the former)) were documented. Histologic findings from colectomy specimens (e.g. dysplasia, cancer) were recorded. For colectomies, only the highest grade of CRN was recorded for the purposes of this study. Thus, an outcome of IND, for example, implies that there was no synchronous diagnosis of LGD, HGD or CRC.

The date of the index colonoscopy was set as the start of follow-up and the time-at-risk. The total duration of follow-up was defined as the interval between the index colonoscopy (t0) and time tx, which was the first occurrence of any of the following events: the primary outcome, any censoring event, or the predefined end of the study period (January 31, 2017). Patients were censored at colectomy, a diagnosis of ACRN, or last follow-up before the end of the study period.

Outcomes of Interest

The primary outcome of the study was the rate of occurrence of ACRN. Secondary outcomes were the rate of occurrence of CRN and colectomy. Furthermore, factors associated with presence or absence of PIPs, and factors predictive of or protective against ACRN and CRN were explored.

Statistical analyses

Descriptive statistics and comparative test statistics were reported according to the distribution of the data. Missing data were interpreted as absence of a characteristic for categorical parameters and excluded for continuous parameters. Time-to-event analyses were conducted for ACRN, CRN (defined as LGD, HGD, or CRC) and colectomy. For analyses of CRN, patients with "prior dysplasia" (defined as IND or LGD diagnosed at or before the index colonoscopy) were excluded. There were no missing data for the primary analyses of (A)CRN. Survival analysis was performed using Kaplan-Meier curves with log-rank test for significance. Patients were censored as defined above. Cox regression analysis was used to identify predictors for ACRN and CRN (hazard rates; HR), both for the joint cohort and stratified by cohort geography (USA versus Dutch cohort). Logistic regression was used instead of Cox regression to identify factors associated with PIPs (odds ratios; OR) since the majority of patients with PIPs had presented with PIPs at the index colonoscopy (i.e. "prevalent cases" instead of "incident cases"). As the primary exposure of interest, PIPs were included *a priori* in all multivariable analyses. PSC was also included *a priori* in all models, as it is an established strong predictor of ACRN.[14–17] In addition, covariates with

P<0.10 on univariable analyses were included in the multivariable models. Interactions between covariates included in the multivariable models and the presence of PIPs were tested by comparing the log-likelihood ratios of the models that included the interaction term with the models that included these covariates as independent variables; no significant interactions were identified. We additionally performed the following time-trend analyses for our primary and secondary outcomes: 1) stratified analysis according to date of index colonoscopy; 2) sensitivity analysis excluding patients with colonoscopies prior to 01/01/2000; and 3) multivariable Cox regression analysis with year of the index colonoscopy included as an independent variable.

Reported HRs or ORs indicate risk or odds, respectively, per unit increase of corresponding parameters (e.g. per 1 year for disease duration). Mean endoscopic and histologic inflammation were collinear; the latter was preferred and included in the regression models.[10] In order to limit the risk of immortal time bias for *incident* cases of PIPs, PIPs were included in the Cox regression models as a time-changing covariate.[18]

Statistical significance was set at a two-tailed *P*-value <0.05. The Bonferroni method was used to correct for multiple testing in independent subgroup analyses where appropriate. All analyses were performed using SPSS version 24 (Armonk, NY: IBM Corp.).

Study oversight

This study was reviewed and approved by the Institutional Review Board (IRB) at MSH. In the Netherlands, this study received exempt status from the IRB as it is exempt from the law of human-bound research.

Results

Patient characteristics

Our search yielded 1582 eligible patients: 429 patients in the USA cohort and 1153 in the Dutch cohort (**Figure 1**). The accrual of the cohort is depicted in **Figure 2**. The median follow-up time was 4.8 (IQR: 2.8 – 6.7) years, providing 8182 patient-years of follow-up. Characteristics of the USA and the Dutch cohorts are compared in **Supplementary table 1**.

Factors associated with PIPs

PIPs were present in 462 (29.2%) patients. Characteristics of patients with versus without PIPs are compared in **(Table 1).** PIPs were prevalent in 300 (19.0%) patients, and incident in 162 (10.2%) patients during follow-up. Among patients with PIPs, 273 (59.1%) had PIPs reported on multiple procedures. Out of 140 patients in the USA cohort with PIPs, 94 (67.1%) were categorized as “few”, while the remaining one-third was categorized as “many”. On multivariable logistic regression analysis histologic inflammation, extensive disease and cohort geography (USA versus Dutch cohort) were each independently associated with presence of PIPs. PSC was independently associated with absence of PIPs (**Table 2**).

Figure 1: Flowchart of patient selection from databases. *Exclusion rate in the Dutch cohort is lower than in the USA cohort, because the majority of ineligible patients were excluded prior to data entry.

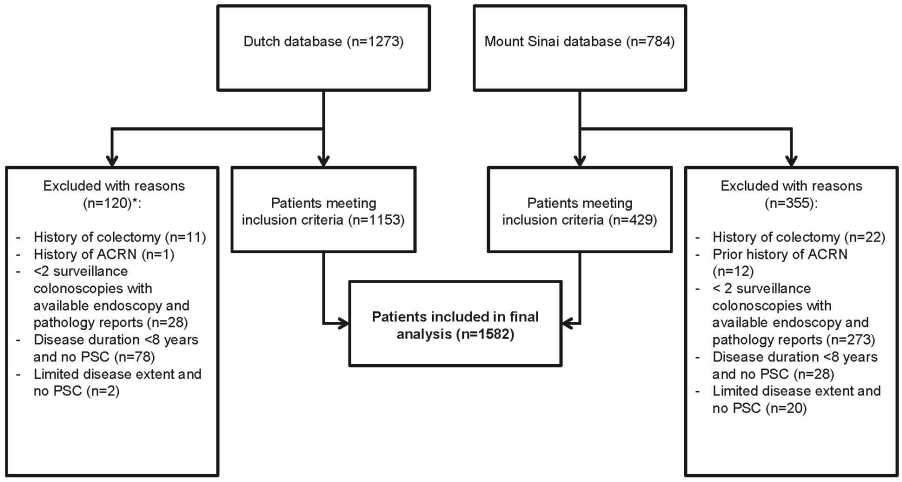


Figure 2: Accrual of the cohort.

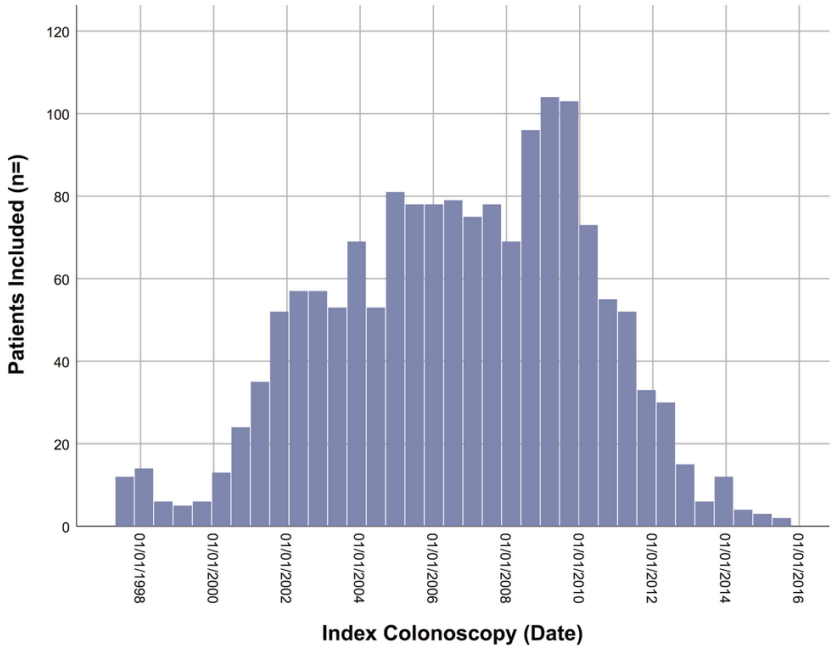


Table 1. *Patient characteristics and follow-up data stratified by presence of PIPs*

	PIPs n=462	No PIPs n=1120	*P* value
Baseline and disease-related characteristics			
Age at index colonoscopy (years), median (IQR)	45 (36 - 56)	45.5 (35 - 54)	0.43
Sex, n (%)			0.42
Male	238 (51.1)	597 (53.3)	
Female	227 (48.9)	523 (46.7)	
IBD type, n (%)	279 (60.4)	230 (53.6)	0.81
Ulcerative colitis	170 (36.8)	181 (42.2)	
Crohn's disease	13 (2.8)	18 (4.2)	
IBD-unclassified			
Incident PIPs, n (%)	162 (35.1)	-	-
Follow-up before first diagnosis of PIPs (years), median (IQR)	2.9 (2.0 – 4.7)		
Family history of Colorectal Cancer, n (%)	29 (6.3)	64 (5.7)	0.67
Disease duration at index colonoscopy (years), median (IQR)	14 (10 – 22)	14 (10 - 22)	0.40
Dysplasia[a] at/before index colonoscopy, n (%)	70 (15.2)	163 (14.6)	0.41
Low-grade dysplasia	34 (7.4)	91 (8.1)	
Indefinite for dysplasia	18 (3.9)	27 (2.4)	
Unspecified	17 (3.7)	45 (4.0)	
Extensive disease, n (%)	396 (88)	879 (83)	0.01*
Primary sclerosing cholangitis, n (%)	38 (8.2)	196 (17.5)	<0.0005*
Exposure to medication			
5-Aminosalicylates	393 (85.1)	893 (79.7)	0.01*
Thiopurines	265 (57.4)	475 (42.4)	<0.0005*
Methotrexate	30 (6.5)	60 (5.4)	0.38
Biologicals	125 (27.1)	196 (17.5)	<0.0005*

Table 1. *Patient characteristics and follow-up data stratified by presence of PIPs (continued)*

	PIPs n=462	No PIPs n=1120	*P* value
Colonoscopic Surveillance Details			
Number of procedures/year, median (IQR)	0.7 (0.6 – 1.0)	0.7 (0.6 – 1.0)	0.49
Mean inflammation score			
Endoscopic	1.50 (1.00 – 2.00)	1.41 (1.00 – 1.80)	0.001*
Histologic	2.60 (2.00 – 3.00)	2.50 (2.00 – 3.00)	<0.0005*
Cecum intubated, mean (SD) % of procedures	86.0 (22.3)	87.4 (22.3)	0.21
Adequate bowel preparation, mean (SD) % of procedures	97.6 (10.5)	98.1 (8.5)	0.09
Duration of follow-up (years), median (IQR)	5.4 (3.3 – 7.6)	4.5 (2.7 – 6.6)	<0.0005*

Classification of PIPs in this table includes both prevalent and incident PIPs. * Significant at *P* <0.05 level. PIPs: Post-inflammatory polyps. a) Patients with HGD at/before the index colonoscopy were excluded.

Neoplastic outcomes according to PIP status

Rate of occurrence of ACRN (primary outcome)

During follow-up, 17 patients (3.7%) with PIPs developed ACRN, compared to 24 (2.0%) without PIPs. There was no significant difference in occurrence of ACRN among patients with versus without PIPs (**Figure 3a,** *P*=0.41)**,** with a median time to ACRN of 3.8 (IQR: 2.1 - 6.3) vs. 4.2 (IQR: 3.0 – 5.3) years, respectively. There was no difference in the rate of ACRN according to the density of PIPs (few versus many, USA cohort only) (**Figure S1,** *P*=0.36); or according to multiple reporting of PIPs (≥ 2 procedures) versus single reporting (1 procedure, *P*=0.41). Statistical non-significance in rates of ACRN between patients with versus without PIPs remained in the following subgroups: UC/IBD-U patients, CD patients, the Dutch cohort, USA cohort **(Figure 3c-f)**, patients with/without PSC and patients with/without prior dysplasia (data not shown; each *P*>0.10).

Table 2 *Factors associated with presence of PIPs, logistic regression analysis*

		Univariable			Multivariable[d]		
Variable	**PIPs (%)**	**OR**	**95% CI**	***P* value**	**aOR**	**95%**	***P* value**
Patients with PIPs, n(%)	462 (100)						
Age at IBD diagnosis	-	1.00	0.99 – 1.01	0.96			
Male sex	238 (51)	1.09	0.88 - 1.36	0.42			
Extensive disease	396 (88)	1.51	1.09 – 2.08	0.01*	1.92	1.34 - 2.74	<0.0005*
USA cohort[a]	140 (30)	1.25	0.98 - 1.59	0.06	1.40	1.04 - 1.88	0.03*
Mean histologic inflammation[b]	-	1.39	1.21 – 1.60	<0.0005*	1.32	1.13 - 1.55	0.001*
Primary sclerosing cholangitis	38 (8.2)	0.42	0.29 – 0.61	<0.0005*	0.38	0.26 – 0.55	<0.0005*
Crohn's disease[c]	170 (37)	1.06	0.84 – 1.32	0.64			
Disease duration at index colonoscopy	-	1.01	1.00 – 1.02	0.13			

*Significant at *P* <0.05 level. PIPs: Post-inflammatory polyps. a) Reference category: Dutch cohort b) Before the first reported PIP c) Reference category: ulcerative colitis/IBD-unclassified. d) 77 patients (15 with PIPs) were excluded due to missing values.

Predictors of ACRN

On multivariable Cox regression analysis, PIPs were not predictive of ACRN **(Table 3)**. PSC, disease duration, prior dysplasia and mean histologic inflammation were independent positive predictors of ACRN occurrence, while cecal intubation was protective against ACRN. On stratified analysis by geographic cohort (USA vs Dutch cohort) and date of index colonoscopy (before versus after 01/01/2005), PIPs similarly did not independently predict ACRN. Furthermore, exposure to thiopurines was a significant, independent predictor of ACRN in the USA cohort only (aHR 0.29; 95%CI 0.09 – 1.00), but not in the combined study cohort. Finally, in a subgroup analysis of patients without prior dysplasia, a diagnosis of LGD during follow-up increased the risk of subsequent ACRN by over 5-fold (aHR 5.04; 95%CI: 2.67-9.52, *P*<0.0005) as compared to patients without incident LGD.

Figure 3: Kaplan-Meier curves, ACRN-free survival and CRN-free survival.

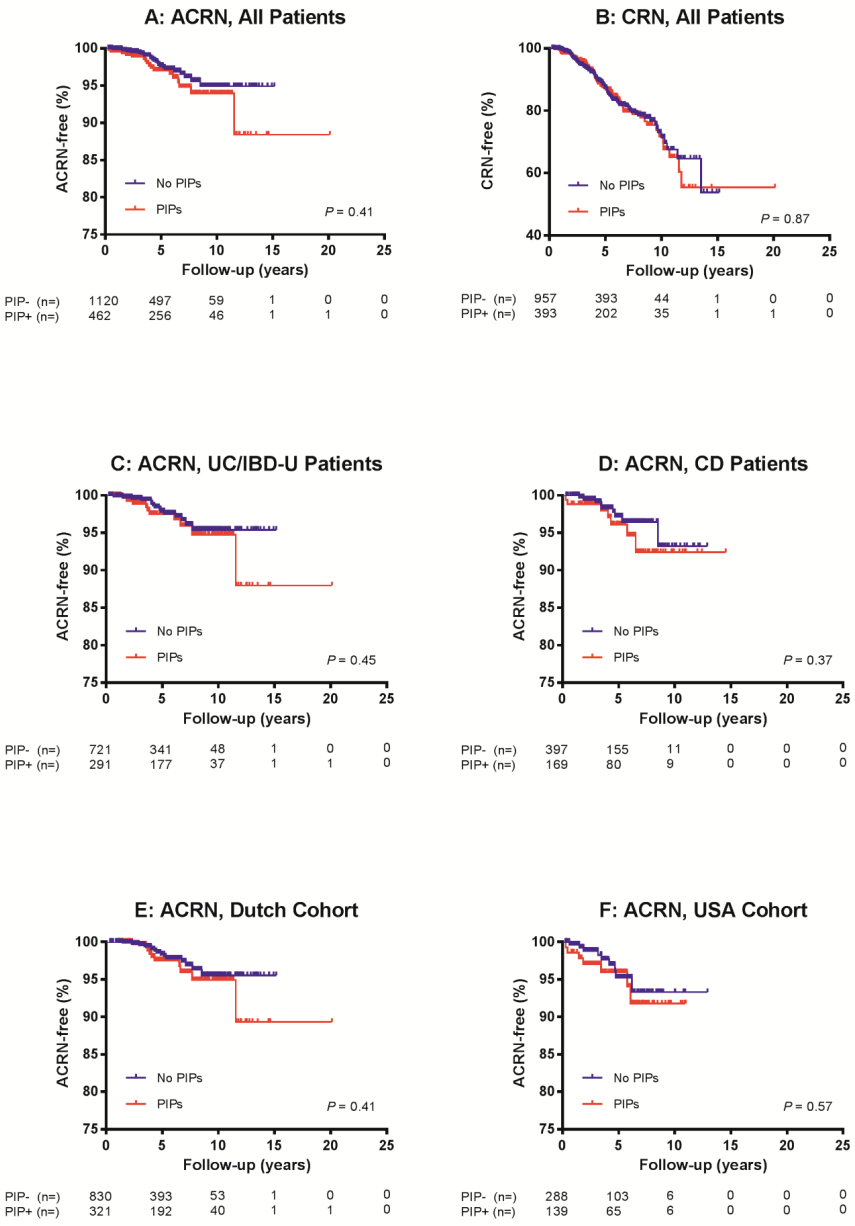


Table 3. *Predictors of ACRN, Cox regression analysis*

		Univariable			Multivariable[e]		
Variable	**ACRN (%)**	**HR**	**95% CI**	***P value***	**aHR**	**95% CI**	***P value***
Total no. of patients with ACRN	41 (100)						
Age at index colonoscopy	-	1.02	0.99 – 1.04	0.17			
Male Sex	27 (65.9)	1.77	0.93 – 3.38	0.08	1.96	0.99 – 3.88	0.06
USA cohort[a]	16 (39.0)	2.41	1.28 - 4.55	0.01*	1.39	0.66 - 2.91	0.39
Presence of PIPs[b]	17 (41.5)	1.56	0.82 - 2.96	0.17	1.17	0.59 - 2.31	0.65
Primary sclerosing cholangitis	9 (22.0)	1.70	0.81 – 3.57	0.16	2.30	1.05 - 5.06	0.04*
Dysplasia at/before index colonoscopy[c]	19 (46.3)	5.92	3.06 – 11.42	<0.0005*	4.89	2.60 – 9.22	<0.0005*
Mean histologic inflammation	-	2.40	1.63 – 3.53	<0.0005*	2.11	1.34 – 3.34	<0.001*
Disease duration at index colonoscopy	-	1.05	1.02 – 1.08	0.003*	1.04	1.01 – 1.08	0.005*
Cecum reached	-	0.11	0.01 - 0.85	0.03*	0.09	0.01 – 0.68	0.02*
Family history of Colorectal Cancer	5 (12.2)	2.32	0.91 – 5.91	0.08	1.94	0.73 – 5.15	0.18
Exposure to 5-Aminosalicylates	38 (92.7)	2.42	0.75 - 7.86	0.14			
Crohn's Disease[d]	16 (39.0)	1.38	0.74 – 2.60	0.31			
Adequate Bowel Preparation	-	1.25	0.27 – 5.69	0.78			
Exposure to biologicals	7 (17.1)	1.05	0.46 – 2.37	0.91			
Number of surveillance colonoscopies	-	0.92	0.78 – 1.10	0.36			
Exposure to thiopurines	-	0.70	0.37 – 1.33	0.27			
Extensive disease	33 (80.5)	0.56	0.26 – 1.22	0.15			

*Significant at *P* <0.05 level. ACRN: Advanced colorectal neoplasia. PIPs: Post-inflammatory polyps. a) Reference category: Dutch cohort. b) Time-changing covariate. c) Indefinite for dysplasia or low-grade dysplasia. d) Reference category: Ulcerative colitis/IBD-unclassified. e) 38 patients (1 ACRN) were excluded due to missing values.

Rate of occurrence of CRN (secondary outcome)

The analyses for CRN were restricted to patients without prior dysplasia (n=1350). As defined previously, CRN is inclusive of LGD, HGD and CRC. During follow-up, 188 patients (13.9%) were diagnosed with CRN, 64 (16.3%) with PIPs and 124 (13.0%) without PIPs. There was no significant difference in the rate of CRN occurrence between patients with PIPs versus without PIPs (**Figure 3b**). Similar to ACRN, time-to-CRN was not significantly different in patients with PIPs reported on multiple procedures (≥ 2) versus on one procedure only (*P*=0.84). Statistical non-significance remained when comparing time-to-CRN in patients with versus without PIPs on subgroup analyses, including: USA cohort, Dutch cohort (**Supplementary Figure S3a-b**), UC/IBD-U patients, CD patients, and patients with versus without PSC (data not shown; all *P*>0.30). PIPs did not independently predict CRN (aHR 1.25; 95%CI: 0.88 – 1.77). Rather, male sex, increasing age, PSC and disease duration were significant positive independent predictors of CRN. Increasing number of surveillance colonoscopies was protective (**Supplementary Table 2**). Similar to ACRN, stratified analyses based on geographic cohort and date of index colonoscopy confirmed that PIPs were not independently associated with CRN. Furthermore, biologicals were independently protective against CRN in the post-2005 subgroup (aHR 0.50; 95% CI: 0.28 – 0.91). No other predictors of CRN were identified by additional time-trend analyses, as described in our methods.

Presence of CRN in biopsied PIPs (descriptive, USA cohort only):

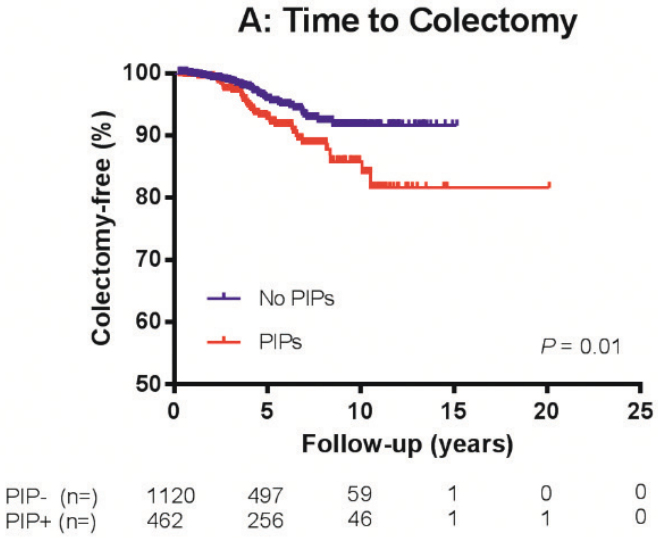
Within the USA cohort, 104 patients (74.2% of patients with PIPs in the USA cohort) had lesions biopsied or resected that were suspected or confirmed PIPs, yielding 360 biopsy jars with histologic data on PIPs. CRN was never detected in a histologically confirmed PIP. In PIPs identified by endoscopy, LGD was found in 3 patients (2.8%) and HGD in 1 (1%), but none of these lesions was histologically confirmed to be a PIP. Additionally, 9 (8.7%) patients were diagnosed with IND in a PIP identified by the endoscopist, of which 6 (66.7%) were histologically confirmed PIPs.

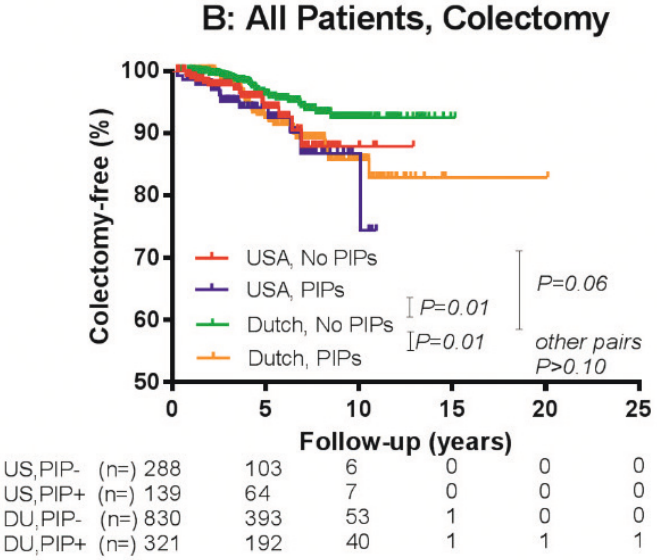
Rate of occurrence of colectomy according to PIP status (secondary outcome)

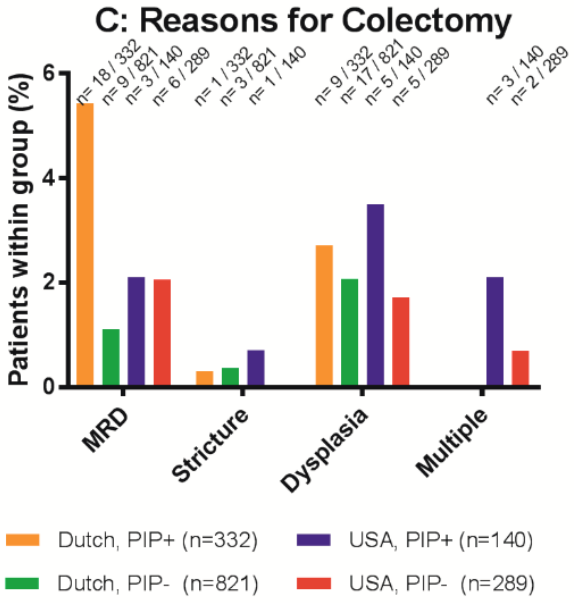
A total of 83 (5.3%) patients underwent colectomy during follow-up. Patients with PIPs more frequently underwent colectomy compared to those without PIPs (8.4% vs. 3.9%) and had a significantly shorter time to colectomy, 3.9 (IQR: 2.6 – 6.3) vs. 4.1 (IQR: 2.5 – 5.1) years, respectively (**Figure 4a,** *P*=0.01). Prior to colectomy, ACRN or CRN had occurred in 26 and 18 patients, respectively. In 39 patients (19 with PIPs and 20 without PIPs; 2.5% of the entire cohort), colectomy was performed before a CRN-related outcome was reached. These patients were censored for the analyses of (A)CRN after a median of 4.2 years of follow-up. We further explored colectomy as an outcome on stratified analysis according to presence versus absence of PIPs and cohort geography (**Figure 4b-c**), and by comparing patients with versus without PIPs among 8 different subgroups (Dutch and USA cohort, CD and UC/IBD-U, patients with and without PSC, index colonoscopy pre- and post-2005). The Bonferroni correction for

multiple testing was employed, resulting in a threshold for significance of $P<0.006$ for comparing patients with versus without PIPs in 8 independent subgroups. Only in the subgroup of CD patients did patients with PIPs versus without PIPs have a significantly higher risk of colectomy (data not shown**,** $P=0.005$), but not in the USA cohort (**Figure 4b**, $P=0.54$), in patients with UC/IBD-U ($P=0.30$), with concomitant PSC ($P=0.02$) or without PSC ($P=0.01$), nor among patients included pre-2005 ($P=0.03$) or post-2005 (data not shown, $P=0.10$). Notably, in the subgroup of Dutch patients, the rate of colectomy was higher in patients with PIPs versus without PIPs (**Figure 4b**, $P=0.008$), but this was statistically nonsignificant after correction for multiple testing. However, when comparing indications for colectomy stratified by PIP status and cohort geography, there was a significant difference in colectomies performed for "medically refractory disease" (MRD) between the groups in **Figure 4c** ($P=0.004$), and specifically between Dutch patients with versus without PIPs ($P=0.001$). No other indications for colectomy were significantly different between the groups.

Figure 4: Kaplan-Meier curves and reasons for colectomy. MRD: medically refractory disease. PIP: post-inflammatory polyp.







Discussion

In this multinational retrospective cohort study of nearly 1600 patients with confirmed colonic IBD undergoing colonoscopic CRN surveillance, PIPs were not a significant independent predictor of dysplasia or CRC. We did find, however, that patients with PIPs had more severe histologic inflammation, more often had extensive colitis, and were significantly more likely to undergo colectomy. Our findings suggest that PIPs are related to the inflammatory burden, but are not themselves a dominant risk factor for CRN.

In contrast, previous studies broadly examining predictors of CRC in IBD reported a significant, independent association between PIPs and CRC.[8,9,11] Limitations of these older case-control studies include selection bias by comparing CRC-patients with low-risk controls, inadequate control for inflammation and less sophisticated endoscopic techniques. Conversely, in this study we utilized a cohort design restricted to patients with confirmed colonic IBD undergoing CRN surveillance and distinctly controlled for histologic inflammation, a well-established predictor of ACRN.[7,10,19,20] Indeed, mean inflammation scores were highly predictive of both ACRN and PIPs in our cohort. Similar to our findings, a recent cohort study of 987 UC patients undergoing CRN surveillance also found that PIPs did not independently predict CRN risk after controlling for cumulative inflammatory burden.[10] In that study, patients with CD or IBD-U were excluded, and only 42 patients with PSC were

enrolled. Further, PIPs were not the primary variable of interest in that study. In our study, we comprehensively evaluate PIPs and utilize sophisticated analytics to address biases relevant to PIPs and CRN. We confirmed that no independent association between PIPs and ACRN exists in a broader population inclusive of patients with CD or PSC. In this context, a novel finding is that PSC was associated with a significantly lower likelihood of PIPs. This underscores the prevailing hypothesis that the phenotype of PSC-IBD colitis is distinct from non-PSC associated IBD colitis, including clinically quiescent disease.[21] Regarding PIPs in Crohn's colitis, data are scarce.[9] By enrolling a substantial number of patients with Crohn's colitis, we provided evidence that PIPs do not independently predict (A)CRN in this group. Because IBD phenotype was not a predictor of (A)CRN we suggest that surveillance intervals should be independent of IBD phenotype.

While PIPs were not predictive of CRN, patients with PIPs did have significantly higher rates of colectomy. A key strength of our study is that all included patients were undergoing surveillance because of either at least 8 years of colonic disease duration or a concomitant diagnosis of PSC. Thus, even though patients with PIPs underwent colectomy more frequently than patient without PIPs, our cohort was universally at-risk for ACRN at inclusion. Furthermore, very few patients underwent colectomy before a CRN-related outcome was reached, and the median follow-up in these patients was only slightly reduced as compared to the entire cohort (4.2 versus 4.8 years, respectively). That said, we concede that early colectomy in patients with PIPs might obscure an increased risk of CRC. Clinically, though, the competing risk of uncontrolled inflammation necessitating colectomy likely outweighs the risk of CRC in such patients. Indeed, in our cohort, patients with PIPs underwent significantly more colectomies indicated for MRD, but not for dysplasia. Moreover, this was found solely in the Dutch cohort. The reasons for this difference between the two geographic cohorts are unclear, but possibly reflect differences in clinical management and threshold for colectomy. While it is certainly possible that those undergoing colectomy for MRD were more at risk for ACRN in the long term, this risk is likely not driven by PIPs themselves, but by the well-established risk factor of colonic inflammation, confirmed also by our findings.[7,19,20,10]

There are some limitations to our study, beyond those that are inherent to retrospective research. Standardized scores were not employed, but there was collinearity between endoscopic and histologic inflammation scores and an association with ACRN, as expected. While we are unable to provide absolute numbers on how often a dysplasia diagnosis was confirmed by a second expert pathologist, this is standard practice at each included institution. Indeed, confirmation of LGD by a pathology expert panel better predicts ACRN.[22] A second limitation is that reporting of PIPs by endoscopists was not standardized. Consequently, PIPs might be disregarded in the context of other pathologic findings (although, anecdotally, we expect such an occurrence to be exceedingly rare in our cohort, particularly on colonoscopies indicated specifically for surveillance). We improved the accuracy of identifying PIPs by including histologic evidence of PIPs where available. Notably, rates of (A)CRN did not differ according to how often PIPs were reported in

colonoscopy reports. Because underreporting of PIPs might underestimate time-at-risk in patients with PIPs, we analyzed PIPs as a fixed parameter in survival analysis, which has the countereffect of overestimating time-at-risk for patients with PIPs. We also analyzed PIPs as a time-changing covariate to account for incident PIPs after the index colonoscopy and minimize the risk of immortal time bias.[18] In both analyses, PIPs still were not independent predictors of (A)CRN. Notably, though, in these same models, histologic inflammation independently predicted ACRN, and increasing number of surveillance colonoscopies was protective against CRN, both findings that are consistent with literature and support the internal validity of our findings.[7,10,19,20,23] All told, substantial misclassification of PIPs seems unlikely, as endoscopists have good interobserver agreement for identifying PIPs based on endoscopic assessment.[24] Regarding density of PIPs and ACRN risk, our study is unfortunately underpowered to draw conclusions regarding this issue. With this caveat, our data do suggest that even extensive PIPs in and of themselves might not grossly increase the risk of ACRN, but certainly inadequate visualization of the colonic mucosa and higher inflammatory burden in this setting are important considerations. Prospective, adequately powered studies are needed to better inform clinical decision-making in this setting.

We further acknowledge some baseline differences between the two national cohorts, including more severe inflammation and higher use of biologicals in the USA cohort. The treatment approach concerning biologicals may be different between the USA and the Netherlands, particularly during the time period of this study when data were still emerging regarding the (cost-)efficacy of biologicals. Alternatively, this difference might also indicate a more severe patient population given that the USA cohort represents a tertiary IBD referral center. In our cohort, exposure to biologicals was protective against CRN and not ACRN, but only in the subgroup analysis of patients included after 2005 (presumably due to the more routine use in this time period). Although this is compelling, our study was not designed to extensively assess the chemoprotective effect of medications, and the literature remains inconclusive regarding the potential chemoprotective effect of biologicals.[25,26] Regardless of these baseline differences between the two geographic cohorts, comprehensive subgroup analyses by country of origin, stratified Cox regression modelling and including country of origin as an independent covariate in the multivariable models showed no modifying or interacting effect on the null association between PIPs and (A)CRN.

Our study has several strengths. One key strength is the large size of our surveillance cohort, with nearly 1600 patients who are well-characterized with respect to clinical, endoscopic, and histologic follow-up data. This large sample size would have allowed us to a detect a clinically relevant hazard rate for both CRN and ACRN. Sample size is of pivotal importance, as ACRN is a rare outcome (incidence of 5.01/1000 patient-years in our surveillance cohort, and also comparable to a recent UC surveillance cohort).[10] Our analyses were robust with no missing data for our primary outcome. We controlled for several relevant covariates including histologic inflammation, as well as evaluated PIPs as a fixed and also a time-changing covariate to account for underreporting of PIPs and immortal time bias,

respectively. That we found already established predictive factors (e.g. inflammation, disease duration, PSC, prior dysplasia) to be independently associated with ACRN supports the internal validity of our study. Furthermore, our findings were essentially validated in two independent surveillance cohorts since neither stratification by geography nor inclusion of geography as a covariate modified the null association between PIPs and our primary and secondary (A)CRN outcomes. It should be highlighted that our cohort reflects a particularly high-risk population for ACRN, with a 14-16% prevalence of PSC and the majority enrolled from tertiary IBD referral centers. Despite this enrichment of potential outcomes, we still did not find an independent association of PIPs with (A)CRN. The lower incidence of ACRN in recent compared to historical IBD cohorts might reflect improved management of patients with high inflammatory potential in our era of "treat-to-target" and "top-down" treatment paradigms. This is highly relevant to our study, as our findings indicate that PIPs are related to more severe and extensive inflammation. With a decreasing incidence of ACRN in most IBD patients, the need for evidence-based risk factors to accurately identify high-risk patients only increases. Utilizing a risk stratification model to guide surveillance intervals is less costly and equally effective as a program without risk stratification.[27]

In conclusion, the current practice of surveillance for CRN is resource-intensive, costly, time-consuming, inconvenient, and likely has a negative impact on the quality of life for patients with IBD. Appropriate categorization of IBD patients according to their risk of CRC as part of an integrated surveillance program with intervals determined by an evidenced-based composite risk score should reduce costs, optimize resource utilization, and maximize patients' quality of life. PIPs have had a reputation of being an ominous risk factor for developing CRN. Our findings should provide some degree of reassurance for clinicians and patients that PIPs are not, in themselves, the worrisome lesions they once were considered. Our data suggest that PIPs are not independently associated with increased risk of any degree of CRN on intermediate-term follow-up, an observation that should be considered in developing future IBD colonoscopic surveillance guidelines.

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Authors names in bold designate shared co-first authorship.

Supplementary table 1. *Patient characteristics and follow-up data stratified by cohort*.

	Dutch Cohort n=1153	USA Cohort n=429	*P* value
Baseline and disease-related characteristics			
Age at index colonoscopy (years), median (IQR)	46 (37 – 54)	42 (31 – 55)	0.002*
Sex, n (%)			0.74
Male	610 (52.9)	223 (52)	
Female	543 (47.1)	206 (48)	
IBD type, n (%)			0.001*
Ulcerative colitis	734 (63.7)	230 (53.6)	
Crohn's disease	387 (33.6)	181 (42.2)	
IBD-unclassified	32 (2.8)	18 (4.2)	
Family history of Colorectal Cancer, n (%)	52 (4.5)	41 (9.6)	<0.0005*
Disease duration at index colonoscopy[a] (years), median (IQR)	15 (11 - 22)	14 (9 - 22)	0.02*
Dysplasia at / before index colonoscopy, n (%)	163 (14.1)	69 (16.1)	<0.0005*
Low-grade dysplasia	96 (8.3)	29 (6.8)	
Indefinite for dysplasia	20 (1.7)	25 (5.8)	
Unspecified	47 (4.1)	15 (3.5)	
Extensive disease, n (%)	1038 (91)	237 (64)	<0.0005*
Primary sclerosing cholangitis, n (%)	165 (14.3)	69 (16.1)	0.38
Medication Exposure, n (%)			
5-Aminosalicylates	911 (79.0)	375 (87.4)	<0.0005*
Thiopurines	495 (42.9)	245 (57.1)	<0.0005*
Methotrexate	61 (5.3)	29 (6.8)	0.26
Biologicals	133 (11.5)	188 (43.8)	<0.0005*
Colonoscopic Surveillance Details			
Presence of PIPs, n(%)	322 (27.9)	140 (32.6)	0.07
Number of procedures/year, median (IQR)	0.7 (0.5 – 0.8)	1.0 (0.7 – 1.3)	<0.0005*
Mean inflammation score			
Endoscopic	1.33 (1.00-1.67)	1.75 (1.33-2.00)	<0.0005*
Histologic	2.33 (2.00-2.80)	3.00 (2.33- 3.50)	<0.0005*
Cecum intubated; mean (SD) % procedures[a]	97.8 (8.9)	98.2 (9.9)	0.15
Adequate bowel preparation; mean (SD) % of procedures	86.7 (21.7)	87,7 (23.8)	0.05*
Duration of follow-up (years), median (IQR)	5.1 (3.1 – 7.3)	4.1 (2.2 – 5.8)	<0.0005*

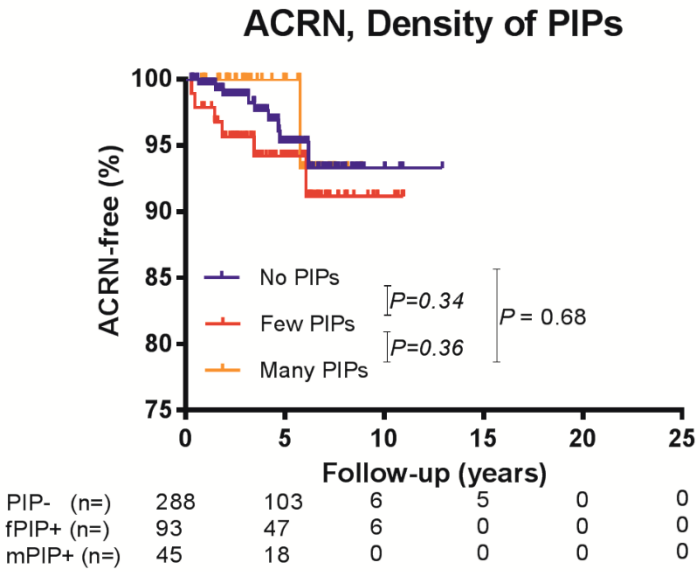
* Significant at *P* <0.05 level. PIPs: Post-inflammatory polyps. a) Patients with HGD at/before the index colonoscopy were excluded.

Supplementary Table 2. *Predictors of CRN, Cox regression analysis*

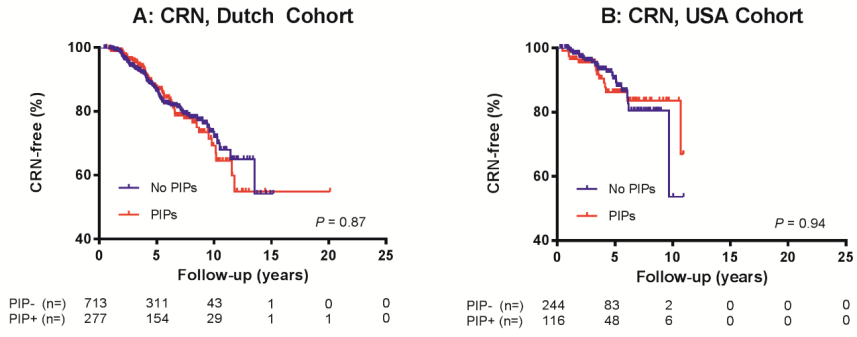
		Univariable			Multivariable[e]		
Variable	**CRN (%)**	**HR**	**95% CI**	***P value***	**aHR**	**95% CI**	***P value***
Patients with CRN, n (%)	188 (100)						
Age at index colonoscopy	-	1.04	1.03 – 1.05	<0.0005*	1.03	1.01 – 1.05	<0.0005*
Male Sex	111 (59.0)	1.39	1.04 – 1.86	0.03*	1.36	1.00 – 1.84	0.05*
Presence of PIPs[a]	64 (34.0)	0.92	0.66 – 1.28	0.61	1.25	0.88 – 1.77	0.21
Primary sclerosing cholangitis	32 (17.0)	1.28	0.87 – 1.88	0.20	2.38	1.58 – 3.58	<0.0005*
Number of surveillance colonoscopies	-	0.58	0.51 – 0.65	<0.0005*	0.54	0.48 – 0.62	<0.0005*
Disease duration at baseline	-	1.03	1.02 – 1.05	<0.0005*	1.02	1.00 – 1.07	0.03*
Exposure to biologicals	22 (11.7)	0.64	0.41 – 1.00	0.05	0.66	0.41 – 1.06	0.09
Extensive disease	156 (83.9)	0.69	0.47 – 1.02	0.06	0.89	0.59 – 1.33	0.57
Family history of Colorectal Cancer	14 (7.4)	1.50	0.87 – 2.58	0.15			
Exposure to 5-Aminosalicylates	167 (88,8)	1.26	0.80 – 1.99	0.31			
Adequate Bowel Preparation	-	1.22	0.61 – 2.42	0.57			
Mean histologic inflammation[b]	-	1.02	0.83 – 1.26	0.87			
Crohn's Disease[c]	58 (30.9)	0.97	0.71 – 1.32	0.83			
USA cohort[d]	36 (19.1)	0.89	0.62 – 1.29	0.54			
Exposure to thiopurines	78 (41.5)	0.89	0.66 – 1.19	0.42			
Cecum reached	-	0.66	0.15 – 2.88	0.58			

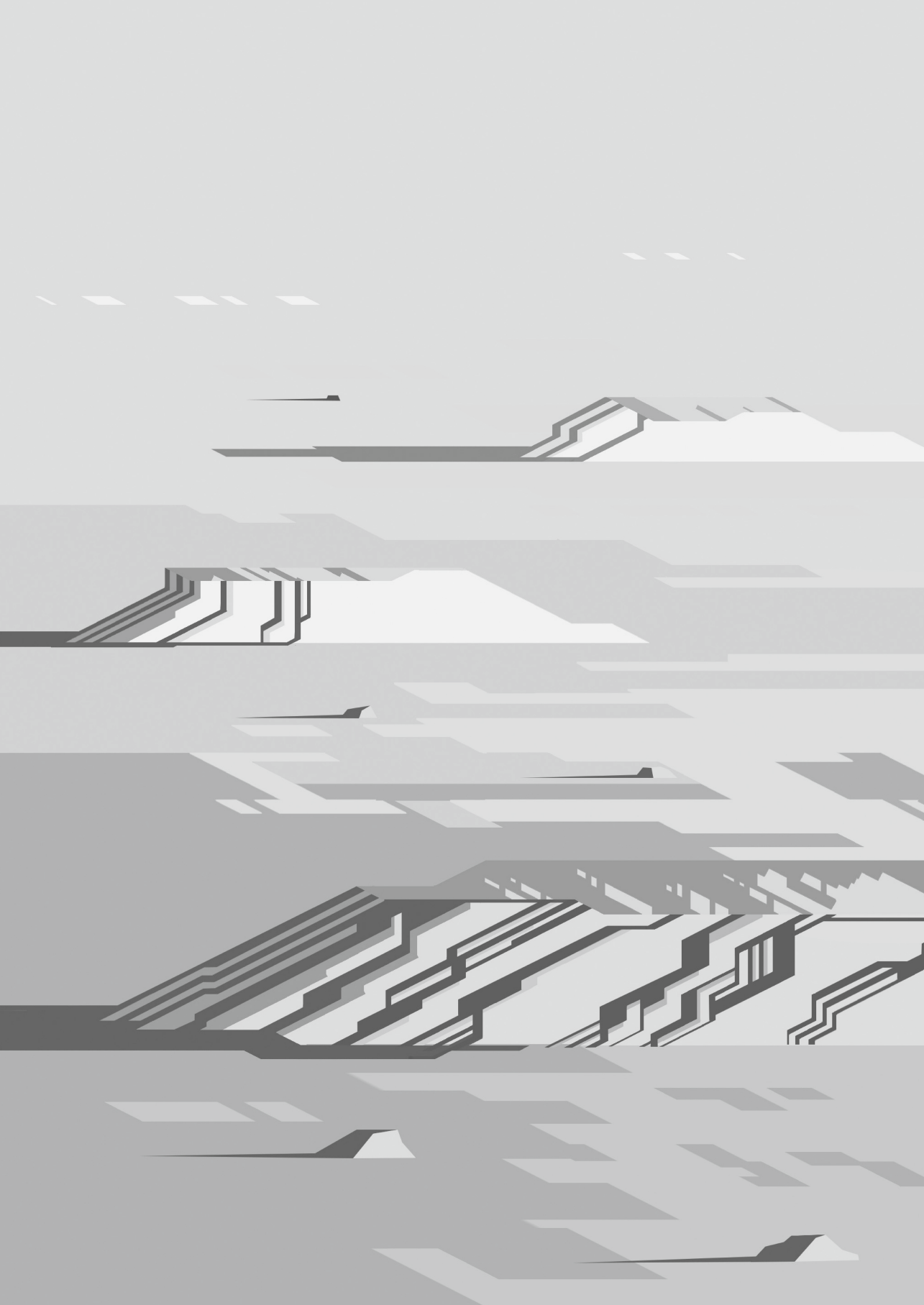
Patients with prior history of colonic dysplasia excluded. *Significant at *P* <0.05 level. CRN: Colorectal neoplasia. PIPs: Post-inflammatory polyps. a) Time-changing covariate. b) Before CRN. c) Reference category: ulcerative colitis/IBD-unclassified. d) Reference category: Dutch cohort. e) 78 patients (5 CRN cases) were excluded due to missing values.

Supplementary Figure 1. Kaplan-Meier curves, ACRN-free survival according to density of PIPs, USA cohort. fPIP: few PIPs. mPIP: many PIPs.



Supplementary Figure 2. Kaplan-Meier curves, CRN-free survival in patients without prior dysplasia, USA and Dutch Cohorts.





Chapter 8

Association Between Indefinite Dysplasia and Advanced Neoplasia in Patients With Inflammatory Bowel Diseases Undergoing Surveillance

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Clin Gastroenterol Hepatol. 2020 Jun;18(7):1518-1527

Abstract

Background and aims
Little is known about the clinical significance of indefinite dysplasia (IND) in patients with inflammatory bowel diseases (IBD) undergoing colonoscopic surveillance for colorectal neoplasia.

Methods
We conducted a retrospective cohort analysis of 492 patients with colonic IBD for 8 or more years or concomitant primary sclerosing cholangitis, with no history of advanced colorectal neoplasia (high-grade dysplasia or colorectal cancer) or colectomy, undergoing colorectal neoplasia surveillance at tertiary IBD referral center from 2001 through 2017. Subjects received consistent histopathologic grading of dysplasia. We collected data on time to development of (advanced) colorectal neoplasia or colectomy using Kaplan Meier methods. We identified factors independently associated with (advanced) colorectal neoplasia with multivariable Cox regression analysis.

Results
After 2149 person-years of follow-up, 53 patients (10.8%) received a diagnosis of IND without prior or synchronous low-grade dysplasia (LGD). Compared to patients without dysplasia, patients with IND had a significantly higher risk of advanced colorectal neoplasia (adjusted hazard ratio, 6.85; 95% CI, 1.78–26.4) and colorectal neoplasia (adjusted hazard ratio, 3.25; 95% CI, 1.50–7.05), but not colectomy (*P*=.78). Compared to IND, LGD was associated with a significantly higher risk of advanced colorectal neoplasia (*P*=.05). Following a diagnosis of no dysplasia, IND only, or LGD, the incidence rates of advanced colorectal neoplasia were 0.4% per patient-year, 3.1% per patient-year, and 8.4% per patient-year, respectively.

Conclusions
In a retrospective analysis of patients with IBD undergoing colorectal neoplasia surveillance with consistent histopathologic grading of dysplasia, IND was independently associated with a significant increase in risk of advanced colorectal neoplasia. These findings require validation and if confirmed, a reappraisal of the colorectal neoplasia surveillance guidelines.

Keywords
Ulcerative colitis, Crohn's disease, carcinogenesis, neoplasm

Introduction

Patients with longstanding colitis due to inflammatory bowel disease (IBD) are at increased risk of colorectal cancer (CRC).[1,2] Surveillance with early detection and management of colorectal neoplasia (CRN; defined as low-grade or high-grade dysplasia [LGD, HGD] or CRC) is universally recommended by major gastroenterological societies.[3–5] There is a large body of evidence establishing the risk of advanced CRN (ACRN: defined as HGD or CRC) following a diagnosis of LGD.[6–8] In contrast, the clinical significance and course of indefinite dysplasia (IND) is less well defined.

A few studies have compared the natural history of IND to no dysplasia (NoD) among IBD patients.[9–13] However, the data are inconclusive due to small sample sizes and unaddressed confounders such as primary sclerosing cholangitis (PSC) and severity of inflammation.[14–17] In the modern era characterized by a vast expansion in medical options to control inflammation, and endoscopic advancements to enhance mucosal visualization, defining the natural history of IND is fundamental to optimizing evidenced-based clinical algorithms for surveillance in IBD.

Our primary objective was to conduct a retrospective cohort analysis of patients with IBD colitis participating in a CRN surveillance program to estimate the risk of ACRN among patients diagnosed with IND, in the absence of prior or synchronous LGD or ACRN, as compared to patients with NoD. Secondary objectives were to estimate the risk of CRN or colectomy among patients with IND, and to compare the risk of ACRN or colectomy between patients with a diagnosis of LGD versus IND.

Methods

Population

We conducted a retrospective cohort analysis of patients with IBD undergoing colonoscopic surveillance between January 2001 - December 2017 at a tertiary IBD referral center (The Mount Sinai Hospital (MSH), New York, NY, United States of America). Eligible patients were identified as described previously.[16,18] Inclusion criteria were: an endoscopically and histologically confirmed diagnosis of IBD (Crohn's disease [CD], ulcerative colitis [UC] or IBD-unclassified [IBD-U]); at least left-sided colonic involvement (UC patients, Montreal classification E2 or E3) or $\geq$30% involvement of colonic mucosa (CD, IBD-U); disease duration of $\geq$ 8 years, or any disease extent or duration in patients with concomitant PSC; an "index" surveillance colonoscopy (defined below) that was followed at least 3 months later by a procedure that allowed for colonic histologic assessment (i.e. at least one subsequent surveillance colonoscopy or colectomy specimen, or any type of procedure yielding a diagnosis of IND or CRN) and; histology analyzed by specialized IBD pathologists at MSH. Patients were excluded if ACRN or colectomy occurred prior to or within 3 months of the index colonoscopy.

Patients with a history of IND or LGD *prior to* the index colonoscopy (henceforth referred to as "prior dysplasia") were not excluded.

Definitions and Classifications

Data were abstracted from the electronic health record (EHR), along with endoscopy and pathology reports according to the definitions described below and in **Supplementary Methods**. No reports or pathology specimens were re-reviewed for the purposes of this study.

Surveillance colonoscopies were defined as procedures with segmental random biopsies or utilization of chromoendoscopy. The "index colonoscopy" was defined as the first surveillance colonoscopy which met the study criteria. The index colonoscopy date was set as the start of follow-up (T0). Surveillance colonoscopies that additionally had adequate quality metrics (good bowel preparation and cecal intubation) were termed "adequate surveillance colonoscopies".

Patients were classified as NoD, IND or LGD according to the criteria in **Supplementary Table 1.** We considered all procedures chronologically (prior history, index colonoscopy and individual follow-up procedures). Only the highest dysplasia grade was considered for each procedure. Once IND or LGD was diagnosed, a patient remained in that category for the rest of the analysis regardless of subsequent findings or absence of findings. If no IND or LGD was diagnosed prior to censoring, a patient was classified as NoD. Thus, "IND" indicates no prior or synchronous LGD. "Prevalent dysplasia" was defined as IND or LGD detected at, or prior to, the index colonoscopy. "Incident dysplasia" was defined as IND or LGD detected at a follow-up procedure in a patient without prior dysplasia or dysplasia at the index colonoscopy.

Histologic assessment

Histologic inflammation was scored on a 5-point scale (1 – normal; 2 – inactive; 3 – mild; 4 – moderate; 5 – severe) modified from the Mount Sinai Division of GI Pathology Histological Activity Index (MSHAI), which has high interobserver agreement.[19–21] Mean histologic inflammation was the mean score of the most inflamed colonic segment from the included surveillance colonoscopies. Histopathological grading of dysplasia was according to the Riddell classification.[22] At MSH, all slides with suspected dysplasia are routinely reviewed by a panel of expert gastrointestinal (GI) pathologists, supervised by one senior GI pathologist (NH).

Outcomes

The primary outcome was ACRN incidence. Secondary outcomes were the CRN or colectomy incidence. We also compared the incidence of ACRN and colectomy among patients with IND versus LGD (secondary analysis).

Statistical analysis

Categorical and continuous variables were compared using the χ^2 or Fisher's exact test and Student *t* or Mann-Whitney U test, respectively. As detailed in **Supplementary methods,** Kaplan Meier curves were generated with log rank tests, while Cox regression modeling was used to identify independent predictors of (A)CRN. Dysplasia was entered as a time-changing covariate that could change from NoD to either IND or LGD over time, but not from IND to LGD. Subgroup analyses were performed for PSC status and for IND patients with, versus without, dysplasia at the second procedure (i.e. the first surveillance colonoscopy after the diagnosis of IND), and sensitivity analyses were performed excluding patients with prior dysplasia and patients with ≤6 months of follow-up. Patients with prevalent LGD were excluded from the analysis of CRN. The Bonferroni method was used to correct for multiple testing in subgroup and sensitivity analyses.

Study oversight

This study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board.

Results

Of 1562 patients with IBD in the MSH surveillance database, 492 patients met the eligibility criteria for analysis (**Supplementary Figure 1**). During 2149 patient-years of follow-up, 32 (6.5%) patients developed ACRN. Fifty-three (10.8%) were categorized as IND, 80 (16.3%) as LGD and 359 (73.0%) as NoD. Among the 53 patients with IND, 15 (28.3%) had IND diagnosed prior to the index colonoscopy, 13 (24.5%) at the index colonoscopy, 25 (47.1%) during follow-up after a median of 3.5 (IQR: 1.9 – 5.4) years. Seven (13.2%) patients were diagnosed with IND at the last available follow-up and excluded from the Kaplan Meier analyses. The proportion of patients classified as IND did not change significantly over time during the study period (**Data not shown, p=0.20**).

Comparison Between IND versus NoD

Patient characteristics

As noted in the Methods section, "IND" refers to IND in the absence of prior or synchronous LGD. Compared to patients with NoD, patients with IND more often had extensive colitis and PSC (**Table 1**). The two groups were similar with respect to mean age, sex, IBD type, disease duration, family history of CRC, and medication exposure. Colonic surveillance was more intensive in patients with IND compared to NoD, as evidenced by more adequate surveillance colonoscopies, more biopsies per procedure, shorter intervals between procedures, increased utilization of chromoendosocopy and slightly longer follow-up (all $p<0.05$). The IND group also had more severe histological inflammation.

Table 1. *Patient characteristics (NoD versus IND).*

	No dysplasia (n=359)	**Indefinite dysplasia** (n=53)	**p value**
Baseline Characteristics			
Age (y), mean (SD)	40.5 (14.9)	44.5 (14.9)	0.07
Male Sex, n (%)	181 (50.4)	32 (60.4)	0.18
IBD-type, n (%) - *UC* - *CD* - *IBDU*	 185 (51.5) 161 (44.8) 13 (3.6)	 30 (56.6) 19 (35.8) 4 (7.5)	0.25
PSC, n (%)	73 (20.3)	17 (32.1)	0.053
Disease duration (y), median (IQR) Extensive colitis, n (%)	11.6 (8.5 – 20.4) 180 (50.1)	12.6 (8.7 – 21.1) 39 (73.6)	0.46 0.001*
Family history of CRC, n (%)	14 (3.9)	3 (5.7)	0.47
Medication exposure, n (%) - *Biologicals* - *Immunomodulators* - *5-Aminosalicylates*	 167 (46.5) 217 (60.4) 317 (88.3)	 22 (41.5) 35 (66.0) 45 (84.9)	 0.50 0.43 0.48
Colonoscopic Surveillance Details			
Duration of follow-up (y), mean (SD)	4.2 (2.5)	5.8 (3.4)	<0.0005*
Number of adequate surveillance colonoscopies, median (IQR)	2.0 (2.0 – 3.0)	3.0 (2.0 – 6.0)	0.006*
Average number of biopsy jars per procedure, median (IQR)	7.3 (5.5 – 8.6)	8.1 (7.3 – 9.4)	<0.0005*
Interval between surveillance colonoscopies (y), median (IQR)	1.24 (0.82 – 1.61)	0.94 (0.68 – 1.27)	0.03*
Procedures with chromoendoscopy, n (% of total number of procedures per group)	29 (2.5)	20 (6.4)	<0.0005*
Mean Histologic inflammation, mean (SD)	2.9 (0.9)	3.4 (1.0)	<0.001*

*Significant.

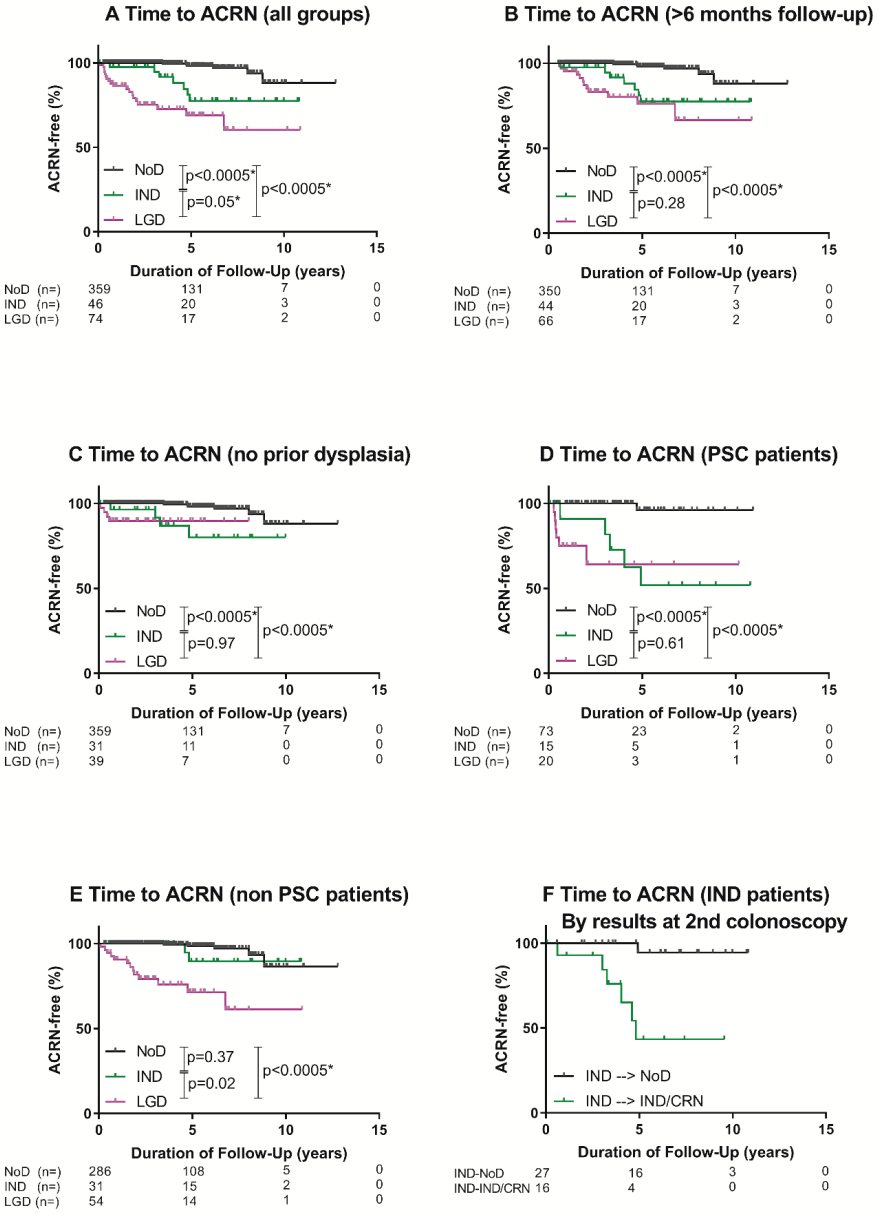
Incidence of ACRN

Compared to patients with NoD, patients with IND had a significantly higher rate of progression to ACRN (**Figure 1a;** p<0.0005). The incidence rate of ACRN was 3.1% per person-year in the IND group and 0.4% per person-year in the NoD group. ACRN developed in 7 (13.2%) patients with IND at a median of 4.0 (IQR 3.0 – 4.8) years after the diagnosis of IND, compared with only 6 (1.7%) patients with NoD at a median of 5.5 (IQR 4.4 – 8.2) years after index colonoscopy.

The more rapid progression to ACRN among patients with IND compared to NoD remained significant when sensitivity analyses were performed for only patients with >6 months of follow-up (**Figure 1b**; p<0.0005) and only patients without *prior* dysplasia (**Figure 1c**; p<0.0005). When analyzing patients with PSC, those with IND (vs. NoD) had a higher risk of progression to ACRN (**Figure 1d**; p<0.0005), but this pattern was not seen in patients *without* PSC (**Figure 1e**; p=0.37).

In those patients who were diagnosed with IND, a subsequent surveillance procedure was performed in 43 patients after a median of 1.1 (IQR 0.81 – 1.57) years. Importantly, if dysplasia was not confirmed on the second procedure – versus confirmation of IND or a higher grade lesion - the risk of ACRN was significantly lower (**Figure 1f**; 0.5% versus 9.9% per patient-year; p<0.0005).

Figure 1. Progression to ACRN.



*significant

Independent predictors of ACRN

Compared to NoD, IND was associated with a 6.85-fold higher risk of ACRN (aHR 6.85; 95% CI 1.78 – 26.4; **Table 2**). Other significant, independent positive predictors of progression to ACRN were LGD (aHR 21.5; 95% CI 5.93 – 77.8) and histologic inflammation (aHR 1.70; 95% CI 1.03 – 2.79), whereas adequate surveillance colonoscopies were protective (aHR 0.49; 95% CI 0.36 – 0.66). There was a trend towards a statistically significant interaction between PSC and the number of surveillance colonoscopies (p=0.053). PSC was an independent predictor of ACRN only when the number of surveillance procedures was omitted from the multivariable model (aHR 2.87; 95%CI 1.14 – 7.20). There were otherwise no significant interactions.

Table 2. *Predictors of ACRN, Cox regression analysis*

		Univariable			Multivariable[4]		
	Events n (%)	**HR**	**95% CI**	**p value**	**aHR**	**95% CI**	**p value**
ACRN, n (%)	32 (100)						
Age	-	1.03	1.01 – 1.05	0.02*	1.03	1.00 – 1.07	0.07
Male Sex	18 (56)	1.16	0.58 – 2.33	0.68	-	-	-
Dysplasia[1]	7 (22)	-	-	<0.0005*	-	-	<0.0005*
- *IND*	19 (59)	8.63	2.79 – 26.7	<0.0005*	6.85	1.78 – 26.4	0.005*
- *LGD*		24.4	9.73 – 61.3	<0.0005*	21.5	5.93 – 77.8	<0.0005*
Prior dysplasia	18 (56)	10.9	5.41 – 22.1	<0.0005*	2.05	0.75 – 5.60	0.16
PSC	12 (38)	2.29	1.12 – 4.68	0.02*	1.14	0.36 – 3.63	0.83
Histologic Inflammation	-	1.77	1.19 – 2.64	0.005*	1.70	1.03 – 2.79	0.04*
Disease duration	-	1.05	1.02 – 1.08	0.001*	1.00	0.96 – 1.03	0.81
Crohn's Disease[2]	10 (31)	0.67	0.32 – 1.41	0.29	-	-	-
Number of adequate surveillance colonoscopies	-	0.55	0.43 – 0.71	<0.0005*	0.49	0.36 – 0.66	<0.0005*
Extensive colitis	23 (72)	1.94	0.89 – 4.21	0.10	1.82	0.74 – 4.44	0.19
Family history of CRC	2 (6)	1.48	0.35 – 6.18	0.59	-	-	-
Exposure to biologicals	10 (31)	0.67	0.32 – 1.43	0.30	-	-	-
Exposure to immunomodulators	13 (41)	0.51	0.25 – 1.04	0.06	0.88	0.37 – 2.09	0.78
Exposure to 5-ASA	25 (78)	0.44	0.19 – 1.03	0.06	0.99	0.34 – 2.93	0.99

1) Time-changing covariate 2) Reference category: UC/IBD-U 3) 16 patients excluded due to missing data. *Significant.

Incidence of CRN and Independent Predictors

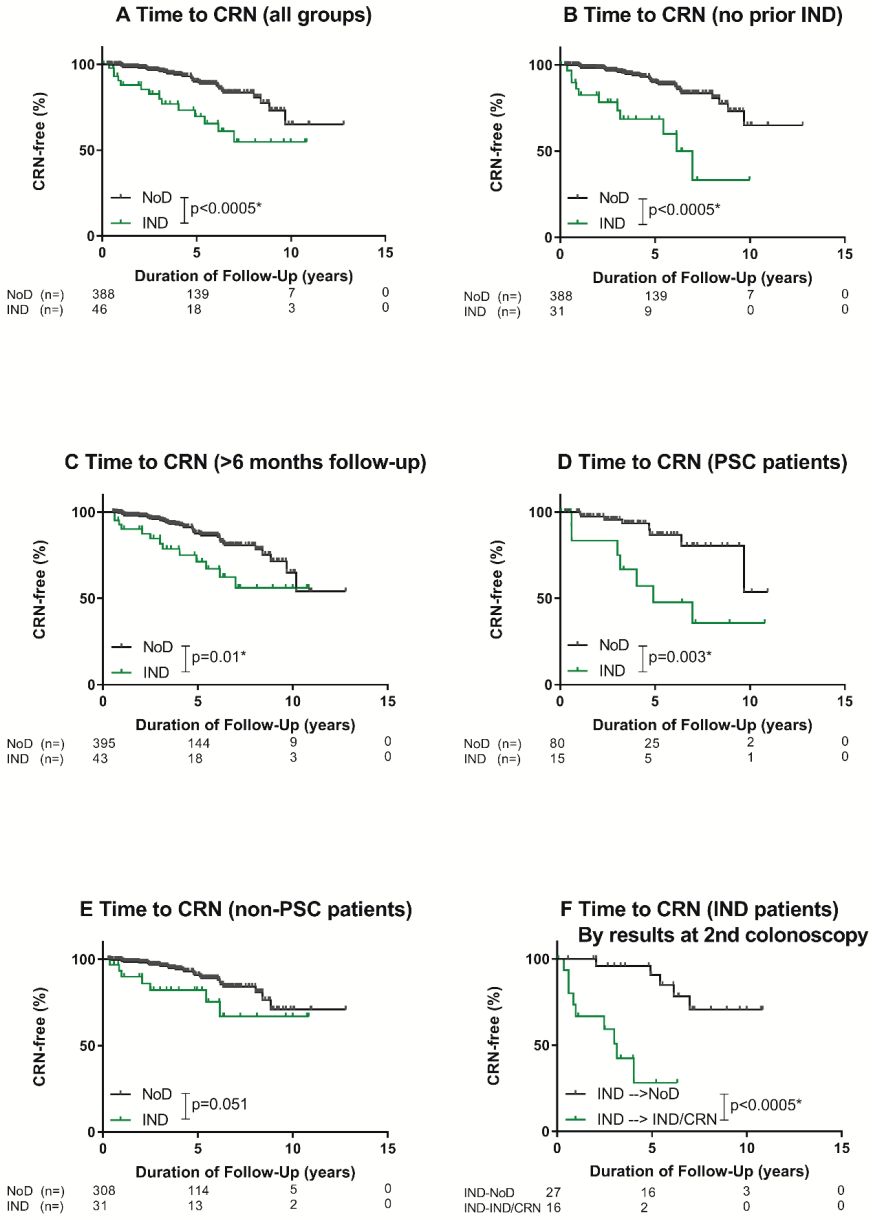
Patients with IND had a significantly higher rate of progression to CRN (LGD, HGD or CRC) compared to patients with NoD (**Figure 2a**; p<0.0005). Fourteen (30.4%) patients with IND developed CRN after a median of 2.75 (IQR: 0.79 – 5.05) years, whereas only 35 (9.0%) patients with NoD developed CRN even after a median of 4.2 (IQR 2.3 – 6.1) years. The incidence of CRN following a diagnosis of IND was 7.0% per patient-year, compared to 2.2% per patient-year in patients with NoD.

The more rapid progression to CRN among patients with IND compared to NoD remained significant when sensitivity analyses were performed for patients without IND prior to the index colonoscopy (**Figure 2b,** p<0.0005), and those with >6 months of follow-up (**Figure 2c,** p=0.01). In the subgroup of patients with PSC, patients with IND had significantly higher rates of progression to CRN compared to patients with NoD, (**Figure 2d,** p=0.003). This was not the case, however, for those without PSC (**Figure 2e,** p=0.051). The Bonferroni-corrected threshold for significance in these analyses was p<0.0125.

IND patients without dysplasia on the subsequent surveillance colonoscopy – compared to those in whom IND or a higher grade lesion was confirmed – had a significantly lower risk of CRN (**Figure 2f**; 3.1% versus 23.3% per patient-year; p <0.0005).

On multivariable analysis, patients with IND had a 3.25-fold (95%CI: 1.50 – 7.05) higher adjusted risk of developing CRN compared to patients with NoD (**Table 3**). No other significant independent predictors of CRN were identified. There were no significant interactions.

Figure 2. Progression to CRN



*significant

Table 3. *Predictors of CRN, Cox regression analysis*

		Univariable			Multivariable		
	Events n (%)	**HR**	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
CRN, n (%)	46 (100)						
Age	-	1.03	1.01 – 1.05	0.003*	1.02	0.99 – 1.04	0.18
Male Sex	23 (50)	1.07	0.61 – 1.88	0.81	-	-	-
IND[1]	14 (30)	2.57	1.33 – 4.95	0.005*	3.25	1.50 – 7.05	0.003*
Prior IND	3 (7)	0.89	0.27 – 2.92	0.85	0.64	0.18 – 2.22	0.48
PSC	15 (33)	1.64	0.89 – 3.02	0.11	1.69	0.81 – 3.50	0.16
Mean Histologic Inflammation	-	1.09	0.79 – 1.51	0.59	1.13	0.77 – 1.65	0.53
Disease duration	-	1.02	1.00 – 1.05	0.07	1.02	0.99 – 1.06	0.21
Crohn's Disease[2]	16 (35)	0.73	0.40 – 1.32	0.29	-	-	-
Number of adequate surveillance colonoscopies	-	1.11	0.97 – 1.27	0.12	1.08	0.93 – 1.24	0.33
Extensive colitis	35 (76)	1.67	0.90 – 3.12	0.11	1.26	0.61 – 2.61	0.53
Family history of CRC	1 (2)	0.46	0.06 – 3.38	0.45	-	-	-
Exposure to biologicals	16 (35)	0.67	0.37 – 1.22	0.19	-	-	-
Exposure to immunomodulators	22 (48)	0.55	0.31 – 0.97	0.04	0.64	0.34 – 1.21	0.17
Exposure to 5-ASA	39 (85)	0.43	0.21 – 0.86	0.02	0.56	0.25 – 1.25	0.16

1) Time-changing covariate 2) Reference category: UC/IBD-U 3) 7 patients were excluded due to missing values. *Significant.

Comparison Between IND versus LGD

Patient characteristics

Compared to patients with IND as the highest grade lesion, patients with LGD more often had longer disease duration, less extensive colitis, less use of immunomodulators, and less severe histologic inflammation (**Supplementary Table 2**). Duration of follow-up was shorter in patients with LGD, but there were otherwise no differences in colonoscopic surveillance details between the groups. IND was significantly less frequently visible, and less frequently polypoid than LGD (**Supplementary Table 3**).[23] IND trended toward more often being unifocal compared to LGD (p=0.052).

Incidence of ACRN

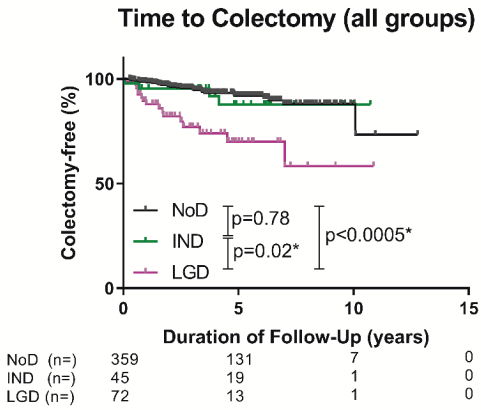
As expected, compared to patients with IND only, patients with LGD had a significantly higher rate of progression to ACRN (**Figure 1a;** p=0.05). ACRN occurred in 19 patients

with LGD (23.8%) at a median of 0.81 (IQR 0.36 – 2.0) years following a diagnosis of LGD, at a rate of 8.4% per person-year. On multivariable analysis, LGD significantly and independently predicted ACRN compared to IND (aHR 3.14; 95%CI 1.02-9.62, based upon the model in **Table 2** with IND instead of NoD as the reference category). However, after correcting for multiple testing (threshold p<0.0125), there was no significant difference in progression to ACRN between patients with LGD versus IND on subgroup or sensitivity analyses (**Figure 1b-e**).

Colectomy incidence and indications

In the IND group, 4 (8.9%) patients underwent colectomy at a rate of 1.9% per patient-year, whereas in the NoD group, 25 (7.0%) patients underwent colectomy at a rate of 1.6% per patient-year. Compared to patients with NoD, patients with IND did not have a significantly higher risk of colectomy (**Figure 3;** p=0.78). While the incidence rate of colectomy was higher among patients with LGD versus IND (7.6% versus 1.9% per patient-year, p=0.02; **Figure 3**), the proportion who had "dysplasia" as the indication for colectomy was 75% in both groups (**Supplementary Table 4**).

Figure 3. Occurrence of Colectomy



*significant.

Discussion

In this retrospective analysis of nearly 500 patients with IBD undergoing colonoscopic surveillance, we report that patients with IND had a significant, and independent, increased risk of ACRN compared to patients without dysplasia. Compared to NoD, IND was associated with a 2.7% per patient-year higher rate of incident ACRN. Furthermore, IND was a significant

independent predictor of CRN, but not of colectomy. This further establishes IND as a clinically relevant, independent risk factor for neoplasia in patients with IBD.

Prior studies reported rates of IND progression to (A)CRN ranging anywhere from 1.0-7.3% per patient-year.[9–13,24,25] In addition to the low incidence of (A)CRN, this wide range may be explained by various limitations. First, unlike the present study, there was variable effort in controlling for established confounders of ACRN, including disease extent and duration,[1] PSC,[16,17] and histologic inflammation.[14,15] Active inflammation and reactive epithelial atypia can be difficult to discriminate from dysplasia, partly explaining why the interobserver agreement among pathologists in the diagnosis of IND and LGD in IBD is poor.[26–29] This is underscored by our finding that patients with IND had more extensive and severe inflammation compared to patients with either NoD or LGD. A critical strength of our study is that we established that IND remained predictive of ACRN even *after* adjusting for histologic inflammation and disease extent. A second limitation of prior studies is that the quality of the histopathological diagnosis of dysplasia differed within, and between, previous studies on IND.[9–13,24,25] In our study, dysplasia was diagnosed by specialized GI pathologists according to the Riddell classification, and confirmed in a peer review setting overseen by an expert pathologist in IBD-associated dysplasia (NH) in order to establish a consensus diagnosis, as recommended by current guidelines.[5,22] Notably, our external validity is supported by results from a large IBD cohort with similar grading of dysplasia, reporting similar progression rates from IND to CRN (6.1% per patient-year versus 7.0% in our study).[13]

Our rigorous analytic approach and attention to relevant sources of bias are other important strengths of this study. The neoplastic risk of IND versus NoD can be overestimated due to immortal time bias, because the start of follow-up differs between the groups (the first colonoscopy versus the diagnosis of incident IND).[30] No prior studies have utilized time-changing covariates to account for this bias.[9,10,12,13] Additionally, we corrected for the frequency and quality of colonoscopic surveillance by adjusting for the number of adequately performed surveillance procedures. Since patients were censored at the last available surveillance colonoscopy or colectomy, absence of dysplasia was reliably confirmed in patients who did not reach the outcome of (A)CRN. Regardless, patients with IND still had a near 7-fold higher risk of ACRN per year compared to NoD.

Our results demonstrated that following a diagnosis of IND, confirmation of IND or CRN on the subsequent colonoscopy predicts the risk of ACRN. In contrast, patients with IND whose subsequent surveillance colonoscopy showed no IND or CRN, had similar risk of ACRN as patients with NoD from the outset (0.5% per patient-year). These findings require external validation. If confirmed, it would seem reasonable to advocate that IND surveillance intervals should be similar to LGD initially with lengthening of the interval if the subsequent colonoscopy shows no dysplasia.

Other novel findings of our study include that IND was significantly less often visible, less often polypoid, and trended towards being more often unifocal compared to LGD. Patients with IND had a significantly lower risk of ACRN compared to LGD on multivariable analysis. These findings are in line with most,[9,12] but not all,[13] prior studies. Unfortunately, insufficient power limited robust sensitivity and subgroup analyses. Notably, among patients who progressed to ACRN, progression occurred more rapidly following a diagnosis of LGD versus IND (median 0.8 versus 4.0 years, respectively).

Our study is not without limitations, mostly inherent to its retrospective design. Patients with a prior history of IND or LGD were not excluded so, in cases where the diagnosis was made outside of MSH, the quality of the histopathological diagnosis could not be guaranteed. However, sensitivity analyses showed that IND predicted (A)CRN independent of prior dysplasia. The data were insufficient to assess the impact of endoscopic resection of lesions. Our cohort, selected from a tertiary IBD referral center, is likely at higher risk for neoplastic progression. The prevalence of PSC was particularly high (especially in patients with IND) and PSC was predictive of ACRN. Although we adjusted for concomitant PSC and established that IND independently predicted (A)CRN, we were not able to confirm specifically that IND predicted (A)CRN in patients *without* PSC. This is most likely explained by the low incidences of IND and (A)CRN in non-PSC patients, but this remains to be confirmed. While there was no significant difference in colectomy rates between the NoD (7%, 25/359) and IND (8.9%, 4/53) groups, this likely reflects insufficient power. More clinically relevant is that the *indication* for colectomy was more often dysplasia/CRC for patients with IND, versus inflammation and/or stricture for NoD patients (not significant). We cannot rule out that some patients who underwent colectomy for non-dysplastic reasons might otherwise have developed (A)CRN on longer follow-up. Because the proportion of patients in the IND and NoD groups undergoing colectomies was similar, this is unlikely to influence the overall conclusions. Lastly, our per-group sample size and low incidence of (A)CRN resulted in wide confidence intervals for the magnitude of the effect of IND on progression to (A)CRN. Future investigations confirming and externally validating our findings are needed. In addition, defining biomarkers for progression from IND to ACRN, such as aneuploidy and p53 overexpression, might be important adjuncts for risk stratification.[25,24,31]

In conclusion, based on a large cohort of patients with IBD undergoing colonoscopic surveillance with consistent grading of all dysplasia, we have established that the diagnosis of IND in itself is an important, independent risk factor for ACRN. We look forward to prospective validation studies since the clinical significance of a diagnosis of IND was heretofore poorly defined. As such, no clinical guidelines have provided clear recommendations for the management of IND.[3–5] In the future, IND should be considered in evidence-based risk-stratification models to guide optimal CRN surveillance and management among patients with IBD.[3,5] Such models would allow for effective surveillance, and thereby limit the physical and psychological burden on patients, as well as societal healthcare costs.

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Supplementary Material

Data collection and Definitions

Baseline and clinical data were abstracted from the EHR using a standardized electronic data collection format in REDCap.[1] These data included date of birth, sex, IBD phenotype, date of IBD diagnosis, family history of CRC (first degree relative), diagnosis of PSC (confirmed by endoscopy, radiology or histology), prior dysplasia and colonic disease extent (maximum extent recorded in the EHR, according to endoscopic and histologic findings). Extensive colitis was defined as inflammation of two-thirds of the colonic mucosal surface for CD, or Montreal classification E3 for UC or IBD-U. Medication history was dichotomized as "any current/prior exposure versus no exposure" and was recorded for the following three classes of IBD-related medications: 5-aminosalicylates, immunomodulators (azathioprine, 6-mercaptopurine and methotrexate) or biologicals (infliximab, adalimumab, certolizumab-pegol, golimumab, ustekinumab, natalizumab or vedolizumab).

Data from surveillance colonoscopies, interval endoscopic procedures (e.g. sigmoidoscopies) and surgical procedures (e.g. colectomies) were collected along with pathology reports. The following data were collected: date and indication of procedure, number of biopsy containers, quality of bowel preparation (adequate [excellent or good] or inadequate [fair or poor]), and whether the cecum was intubated. For each patient, the total number and percentage of surveillance colonoscopies with adequate bowel preparation and cecal intubation was calculated (i.e. *adequate* surveillance colonoscopies). The presence of endoscopically visible lesions was recorded and these were classified *post hoc* as polypoid versus non-polypoid according to SCENIC guidelines, based on the endoscopy reports.[2]

The term "progression" indicates the occurrence of more advanced neoplasia over time in a patient, e.g. IND to LGD or LGD to ACRN, and encompasses both progression of individual lesions and occurrence of additional, more advanced lesions at other anatomically distinct locations.

Statistical analysis

Kaplan Meier curves were generated with log rank tests, while Cox regression modeling was used to identify independent predictors of (A)CRN. Time at risk for progression was initiated at the diagnosis of IND or LGD for patients with *incident* dysplasia, and at the index colonoscopy for patients with NoD or *prevalent* dysplasia. Patients were censored at the outcome of interest (ACRN for primary analysis, CRN or colectomy for secondary analyses), or last available surveillance colonoscopy or colectomy. Patients with IND or LGD diagnosed at the last available procedure were excluded from the Kaplan Meier analysis, unless this was the outcome of interest.

Cox regression modeling was used to identify independent predictors of (A)CRN. Log-log plots were used to assess the proportional hazards assumption of time-static covariates. Dysplasia was entered as a time-changing covariate that could change from NoD to either IND or LGD over time, but not from IND to LGD. Previously established predictors of ACRN (PSC, histologic inflammation, disease extent, disease duration, number of adequate surveillance colonoscopies and prior dysplasia) and variables with $p<0.10$ on the univariable analysis were included in the multivariable model. Interactions between dysplasia and other covariates were tested by comparing log-likelihood ratios of the multivariable models with, versus without, the interaction term. Patients with missing data for covariates included in the multivariable model were excluded (<5% of patients).Statistical analyses were performed using SPSS Statistics 25.0 (IBM Corp., Armonk, N.Y., USA).

Supplementary References

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Supplementary Table 1. *Criteria for classification as NoD, IND or LGD*

Category for analysis	Prior history	Findings at index colonoscopy (prevalent dysplasia)	Findings at first follow-up procedure with IND/LGD (incident dysplasia)	Possible findings at subsequent procedures
NoD	NoD	NoD	not applicable	NoD
IND	Prior IND allowed **AND** No prior LGD	IND, or prior IND **AND** No prior or synchronous LGD	IND **AND** No prior or synchronous LGD	NoD, IND or LGD
LGD	Prior LGD allowed	LGD **OR** prior LGD	LGD **OR** Synchronous IND and LGD	NoD, IND or LGD

Supplementary Table 2: *Patient characteristics (IND versus LGD).*

	Indefinite dysplasia (n=53)	**Low-grade Dysplasia** (n=80)	**p value**
Baseline Characteristics			
Age (y), mean (SD)	44.5 (14.9)	49.0 (15.0)	0.09
Male Sex, n (%)	32 (60.4)	46 (57.5)	0.74
IBD-type, n (%)			0.04*
- *UC*	30 (56.6)	51 (63.7)	0.41
- *CD*	19 (35.8)	29 (36.3)	0.96
- *IBD-U*	4 (7.5)	0 (0)	0.02*
PSC, n (%)	17 (32.1)	20 (25.0)	0.38
Disease duration (y), median (IQR)	12.6 (8.7 – 21.1)	17.4 (9.9 – 30.7)	0.03*
Extensive colitis, n (%)	39 (73.6)	35 (43.8)	0.001*
Family history of CRC, n (%)	3 (5.7)	5 (6.3)	1.00
Medication exposure, n (%)			
- *Biologicals*	22 (41.5)	23 (28.7)	0.13
- *Immunomodulators*	35 (66.0)	33 (41.3)	0.005*
- *5-Aminosalicylates*	45 (84.9)	68 (85.0)	0.99
Time of first diagnosis of dysplasia			
Prior to index colonoscopy, n (%)	15 (28.3)	35 (43.8)	0.07
- *IND*	15 (28.3)	2 (2.5)	
- *LGD*	-	32 (40.0)	
- *Unspecified*	-	1 (1.3)	
At index colonoscopy, n (%)	13 (24.5)	16 (20.0)	0.54
Incident dysplasia during follow-up, n (%)	25 (47.2)	29 (36.3)	0.21
Colonoscopic surveillance details			
Duration of follow-up (y), mean (SD)	5.8 (3.4)	4.2 (2.9)	0.005*
Number of adequate surveillance colonoscopies, median (IQR)	3.0 (2.0 – 6.0)	3.0 (2.0 – 4.0)	0.39
Average number of biopsy jars per procedure, median (IQR)	8.1 (7.3 – 9.4)	8.0 (6.2 – 9.5)	0.33
Interval between surveillance colonoscopies (y), median (IQR)	0.94 (0.68 – 1.27)	0.93 (0.51 – 1.27)	0.36
Chromoendoscopy used[1], n (%)	20 (6.4)	91 (24.9)	<0.0005*
Mean Histologic inflammation, mean (SD)	3.4 (1.0)	2.7 (1.0)	<0.0005*

*Significant at p<0.05. 1) Number of procedures with chromoendoscopy with percentage of total number of procedures.

Supplementary Table 3. *Lesion Characteristics, patients without prior dysplasia only*

	Indefinite dysplasia (n=38)	**Low-grade dysplasia** (n=45)	**p value**
Age at exam with dysplasia	46.5 (14.8)	49.9 (15.1)	0.31
Disease duration at exam with dysplasia	17.0 (7.8)	21.4 (12.4)	0.06
Chromoendoscopy used, n (%)	1 (2.6)	5 (11.1)	0.06
Multifocal dysplasia	5 (13.2)	14 (31.1)	0.052
Visible lesion	7 (18.4)	38 (84.4)	<0.0005*
- *Polypoid lesion*	5 (13.2)	32 (71.1)	<0.0005*
- *Non-polypoid lesion*	0 (0)	5 (11.1)	0.06
- *Stricture*	1 (2.6)	1 (2.2)	1.00
- *Unknown*	1 (2.6)	0 (0)	-

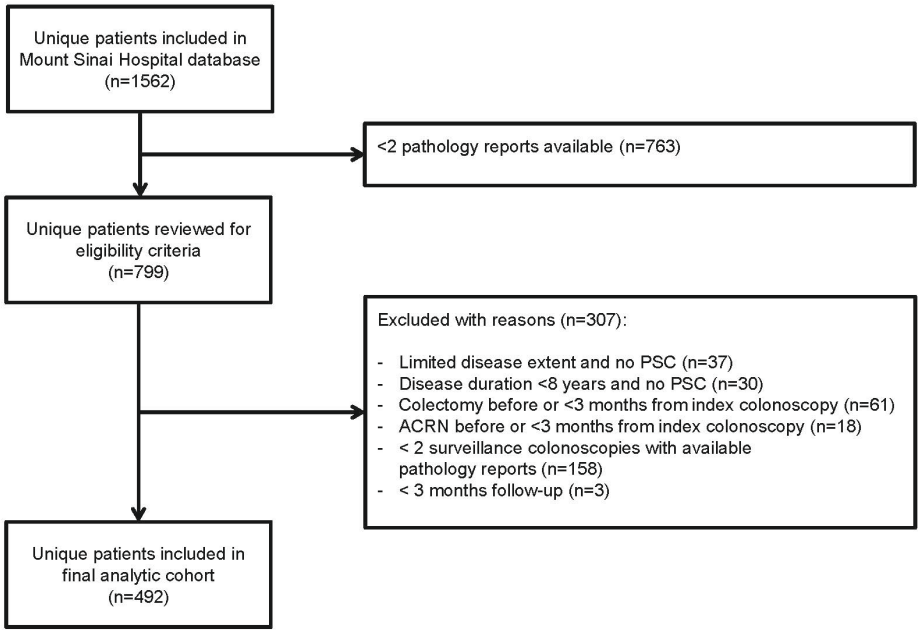
* Significant at p<0.05.

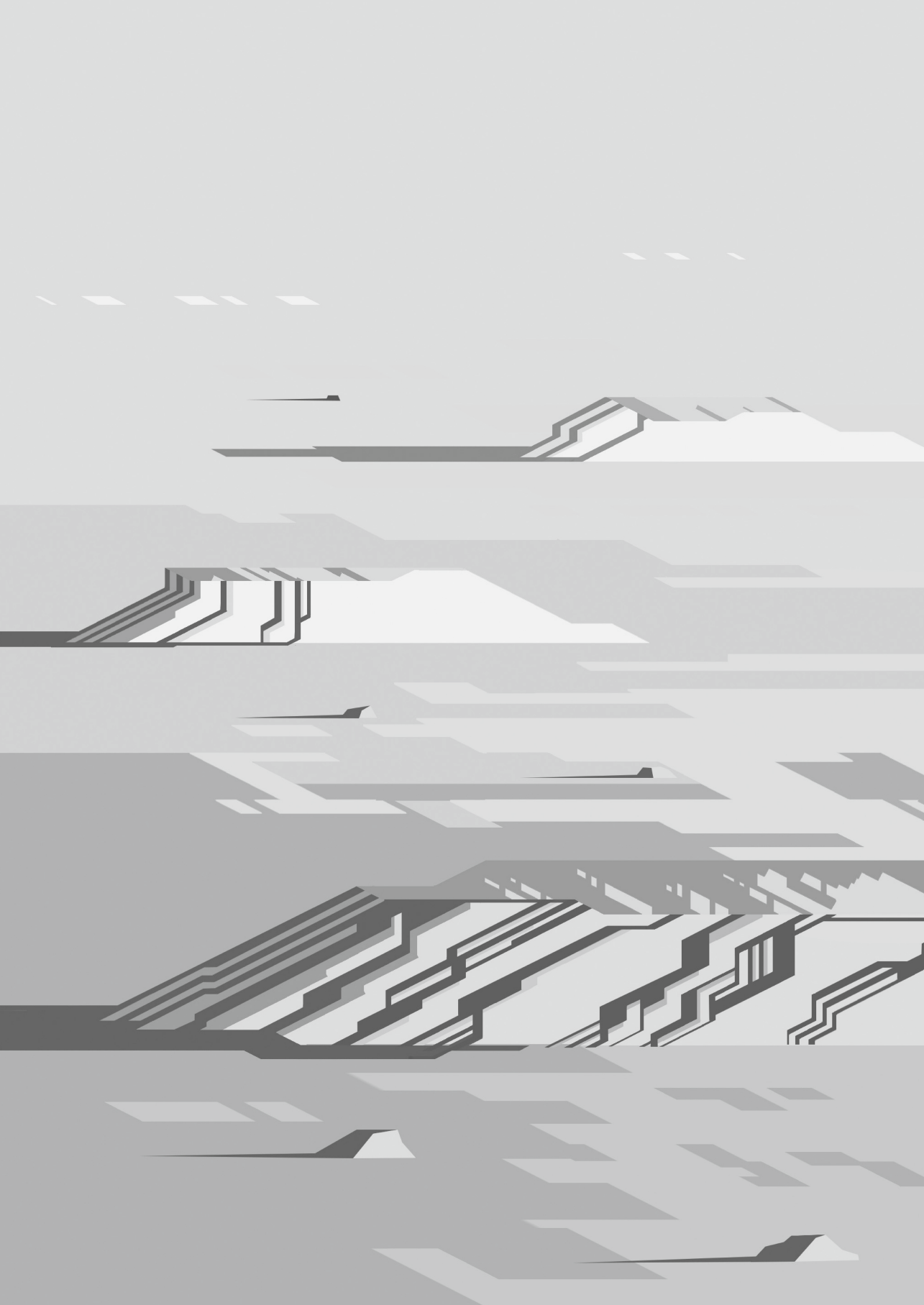
Supplementary Table 4. Indications for colectomy (NoD versus IND versus LGD)

	NoD (n=359)	**IND** (n=53)	**LGD** (n=72)	**p value**
Colectomy (n, %)	25 (7.0)	4 (8.9)	16 (22.2)	<0.0005*
Indications for colectomy				
Dysplasia or CRC	2 (0.6)	3 (6.7)	12 (16.7)	<0.0005*
Inflammation	15 (4.2)	1 (2.2)	2 (2.8)	0.59
Stricture	2 (0.6)	0 (0)	0 (0)	0.72
Inflammation + stricture	6 (1.7)	0 (0)	0 (0)	0.37
Unknown	0 (0)	0 (0)	2 (2.5)	-

*Significant at p<0.05.

Supplementary Figure 1. Selection of eligible patients





CHAPTER 9

GENERAL DISCUSSION

General Discussion

Long-term management of inflammatory bowel disease (IBD) should aim to prevent disease recurrence and complications, while minimizing the risks, burden and costs of the treatments that patients with IBD are exposed to along the way. Ambitious treatment targets such as endoscopic healing improve long-term outcomes but might require early escalation to advanced therapies, including anti-tumor necrosis factor-alpha (anti-TNF) agents. **Section I** of this thesis focused on long-term maintenance treatment with anti-TNF agents and the possibility of treatment de-escalation after establishing disease remission.

IBD patients with colonic inflammation are at an increased risk of developing colorectal cancer. Endoscopic surveillance aims to reduce the risk of colorectal cancer. The risk-stratified approach currently used to determine the surveillance interval may be improved to increase the efficacy of endoscopic surveillance. **Section II** of this thesis focuses on risk factors for developing colorectal cancer in patients with IBD. Although important knowledge gaps persist, this thesis is a modest step forward towards an evidence-based strategy for management of IBD beyond the immediate suppression of active inflammation.

SECTION I. Maintenance therapy with anti-TNF therapy and therapeutic de-escalation

Ambitious treatment targets may alter the disease course of IBD

During the last decades, recommended short- and long-term treatment targets for patients with IBD have become increasingly ambitious. In 2021, the STRIDE-II, an updated multinational consensus statement on treatment targets for patients with IBD was published.[1] According to the STRIDE-II, in addition to a symptomatic response, long-term treatment targets should include objective endpoints, including biomarker normalization (C-reactive protein [CRP] and fecal calprotectin) and endoscopic healing. More research is ongoing to include histologic and radiologic (transmural) remission as formal treatment targets. This includes randomized controlled trials (RCTs) that evaluate the efficacy of a treatment *strategy* rather than the efficacy of a single treatment agent.

Evidence supporting the use of strict criteria for remission is emerging. A large meta-analysis reported that patients with ulcerative colitis (UC) in clinical remission and complete endoscopic healing (Mayo 0) had a lower relapse risk than those with mild persistent inflammation (Mayo 1). The risk of relapse was even lower among patients who were also in histologic remission.[2] The strategic VERDICT RCT (NCT04259138) will examine histologic remission as an optimal treatment target. In this still ongoing RCT, patients with moderate-to- severe active UC are randomized to treatment escalation based on symptoms alone (absence of rectal bleeding), symptoms and endoscopic healing, or a combination of symptoms, endoscopic healing and histologic healing.

In Crohn's disease (CD), multiple observational studies have confirmed that objective remission (biomarkers or endoscopy) is associated with long-term remission and fewer CD-related complications, surgeries and hospitalizations.[3–5] In addition, outcomes of strategic RCTs in CD have been reported. The CALM RCT corroborated the concept that treatment escalation in patients on adalimumab therapy based on a *tight control* strategy (steroid-free clinical remission with normalization of CRP and fecal calprotectin) improved clinical and endoscopic outcomes, compared with routine care (treatment escalation based on steroid-free clinical remission).[6] In the REACT study, early initiation of anti-TNF therapy combined with immunomodulators (thiopurines or methotrexate) resulted in fewer hospitalizations, surgical resections and CD-related complications, compared with standard care.[7] In contrast, in the recent STARDUST trial, dose escalation of ustekinumab based on strict criteria (endoscopy, CRP and fecal calprotectin) versus symptoms alone did not improve clinical and endoscopic outcomes at one year.[8] While this may undermine the evidence in favor of a tight control strategy, it may also suggest that in case of insufficient response to ustekinumab, dose escalation is not as effective as with anti-TNF agents.

Ambitious treatment targets lead to increased medication use

Ambitious treatment targets are a blessing and a curse. As described above, treatment escalation based on objective criteria may decrease morbidity in patients with IBD in the long run. However, evaluation of endoscopic or histologic remission requires invasive diagnostic procedures. In the STARDUST and VERDICT trials, patients undergo 3 to 4 endoscopies within one year, respectively, which may be unacceptable for patients and limits the translation of such trials designs to clinical practice.

Treatment escalation based on endoscopy or biomarkers also leads to increased exposure to advanced therapies, including anti-TNF agents. For example, by end of the CALM study, 45% versus 14% of patients were escalated to weekly adalimumab in the tight control versus standard care arms, respectively.[6] With increasing numbers of patients with IBD on advanced therapies, treatment costs and (rare) side effects become ever more important. For anti-TNF therapy, side effects include serious infections[9], melanoma[10] and lymphoma.[11] In addition, biological therapy is expensive. In the Netherlands, infliximab and adalimumab were ranked 3rd and 4th in the list of most expensive drugs with total costs of 89.3 and 89.1 million euros in 2019 (for all indications), even while biosimilars for infliximab and adalimumab were already available.[12]

Thus, treat-to-target strategies may lead to increased use of IBD drugs contributing to more side-effects and higher costs. De-escalation strategies may result in the opposite.

De-escalation of medical therapy for IBD patients in remission

In this thesis, de-escalation of medical therapy is defined as elective discontinuation of maintenance treatment in patients with IBD in remission, with the aim to meet patient preferences and limit treatment-related side effects and costs. This may provide a complementary, more sustainable, long-term strategy to a tight control strategy, provided that the risk of relapse after de-escalation of medical therapy is acceptable. The topic of de-escalation of anti-TNF therapy and/or immunomodulators is central to **Section I** of this thesis. Withdrawal of the immunomodulator from anti-TNF combination therapy is discussed in **Chapter 4**. Withdrawal of anti-TNF treatment is evaluated in **Chapter 2 and 3. Chapter 5** provides real-world data of long-term anti-TNF treatment and reasons for treatment withdrawal in two hospitals in the Netherlands between 2011 and 2019.

Can we de-escalate immunomodulators?

Treatment with anti-TNF agents, including infliximab and adalimumab, is an effective strategy to induce and maintain remission in patients with IBD.[13–16] Furthermore, combining infliximab with an immunomodulator (thiopurine or methotrexate) is even more effective than monotherapy.[17] The clinical benefit of combining adalimumab with an immunomodulator is not unequivocal.[18] However, both for infliximab and adalimumab treatment, concomitant immunomodulator use decreases the risk of anti-drug antibody formation.[19] According to our data, the majority of patients in the Netherlands receive anti-TNF combination therapy (79% for infliximab and 59% for adalimumab, **Chapter 5**). Of note, more than 90% of the patients in our cohort received a thiopurine.

Unfortunately, the combination of anti-TNF with a thiopurine does not only increase efficacy but also increases toxicity. Combination therapy is associated with a 1.2-fold increased risk of hospitalization due to a serious infection.[9] Rare but potentially life threatening, the increased risk of malignant lymphoma with anti-TNF combination therapy is concerning. The absolute lymphoma risk increases stepwise from 0.26 to 0.41 and 0.95 per 1000 patient-years between unexposed patients, patients receiving anti-TNF monotherapy, and those receiving combination therapy with an immunomodulator. After adjustment for confounders, patients using anti-TNF combination therapy are at a 2.5-fold or 6.1-fold increased risk of lymphoma compared with anti-TNF monotherapy or no therapy, respectively.[11] In clinical practice, immunomodulators are frequently discontinued from maintenance therapy to mitigate the risks of malignancy and infections, but limited evidence is available to support this strategy. Three small RCTs directly compared immunomodulator withdrawal versus continuation and detected no significant differences in the risk of relapse, but these studies were underpowered.[20–22]

In the large cohort study presented in **Chapter 4**, we compared immunomodulator withdrawal (n=296) versus continuation (n=318) among patients using anti-TNF combination

therapy in routine clinical practice. Immunomodulator withdrawal did not increase the risk of loss of response to anti-TNF therapy, defined as stopping anti-TNF therapy due to loss of efficacy. Since this was a retrospective study, there is a risk of bias as physicians may be more likely to stop immunomodulators in patients who are expected to remain in remission. This decision is often based on subjective criteria, that are not reflected in the measurable confounders included in the analysis of this study. Fortunately, additional data are available to support the concept of immunomodulator withdrawal. Recently, our results were corroborated by the large SPARE RCT, in which azathioprine withdrawal in CD patients in remission with infliximab and azathioprine did not increase the risk of symptomatic flares.[23] Our study in **Chapter 4** confirms that the results of these RCTs can be translated to a broader "real world" patient population.

Evaluation of symptoms, CRP, fecal calprotectin and anti-TNF trough levels may be warranted prior to immunomodulator discontinuation, as these were all predictive of loss of response following immunomodulator withdrawal in our study. We did observe lower anti-TNF trough levels and an increased risk of anti-drug antibodies after immunomodulator withdrawal. Therefore, monitoring of anti-TNF trough levels and anti-drug antibodies may be of added value after immunomodulator withdrawal. A longer duration of combination therapy mitigated the risk of anti-drug antibodies. In selected patients with a complicated disease history and with limited treatment options, continuation of immunomodulators can be considered. In general, however, immunomodulator withdrawal from anti-TNF combination therapy among patients in remission seems feasible and safe in patients with IBD.

Withdrawal of anti-TNF treatment: a complicated STORI

Withdrawal of anti-TNF treatment in patients with IBD is more controversial, due to a substantially higher risk of relapse.[23–25] The prospective STORI trial reported a risk of relapse after withdrawal of anti-TNF therapy of approximately 50% within 1-2 years, and this has been confirmed by other studies.[26,27] Fortunately, 80% of patients will regain remission with anti-TNF reintroduction.[27] Most physicians are cautious to advise patients in remission to discontinue anti-TNF treatment. In our Dutch cohort in **Chapter 5**, only 58 out of 844 (6.9%) episodes of anti-TNF treatment were stopped electively as a de-escalation strategy. Elective withdrawal of anti-TNF therapy is of interest because of its potential to improve patients' quality of life and safety, but only if the risk of relapse is acceptable. In addition, the question of whether the costs of the therapy weigh up to the benefits of long-term treatment cannot be left unanswered.

Withdrawal of anti-TNF: the health-economic perspective

In this thesis, we started by further exploring the rationale for withdrawal of anti-TNF. In **Chapter 2** we analyzed whether withdrawal of anti-TNF treatment in patients with UC in remission is a cost-effective strategy. Due to lack of prospectively collected data, we

constructed a Markov model – integrating data from prior empirical studies. An expert panel was consulted to fill in data points for which no prior literature was available. Of note, our study was conducted after the introduction of biosimilars, which has decreased the costs of anti-TNF therapy. A similar modeling study has been performed for anti-TNF withdrawal in patients with CD.[28] Very briefly, both studies conclude that stopping anti-TNF therapy in IBD patients in remission has the potential to be cost-effective. Stopping anti-TNF therapy decreases costs, even when accounting for the necessity of introducing advanced therapies or surgery in patients who relapse, with a limited impact on the quality of life at a population level.[28,29]

Obviously, modeling studies cannot fully grasp the complexity of reality. The cost-effectiveness of anti-TNF withdrawal depends on numerous factors. Organization of healthcare systems and the availability of biosimilars all have a large impact on healthcare costs. Both studies provide a health care provider perspective and do not include indirect costs, such as loss of productivity. Quality of life is notoriously difficult to quantify. From an ethical perspective, it is questionable whether actively stopping a therapy in order to reduce costs is morally justified. The quality of life of a few individual patients may be disproportionally affected, especially patients not responding to anti-TNF reintroduction after a relapse.

Nevertheless, these modeling studies do show that there is a financial rationale to further explore withdrawal of anti-TNF in IBD patients in remission. Modeling studies also provide insight into parameters that are crucial to consider prior to anti-TNF withdrawal. To further study the effects of withdrawal of anti-TNF therapy, and identify predictors for success, we performed a prospective study, described in **Chapter 3.**

Withdrawal of anti-TNF treatment: the clinical perspective

In this multicenter prospective cohort study (**Chapter 3)** patients with confirmed clinical and endoscopic remission who electively discontinued anti-TNF treatment were included. Despite these strict inclusion criteria, 40% of patients relapsed within 1 year, in line with prior studies.[27] The main finding of our study was that patients with complete endoscopic healing (SES-CD score <3, Mayo score 0) were at lower risk of relapse than those with incomplete endoscopic healing (SES-CD score 3-4 or Mayo 1). In other words, minimal endoscopic inflammation in asymptomatic patients was still associated with a higher risk of relapse after withdrawal of anti-TNF therapy. This finding should be interpreted with some caution because the number of patients without endoscopic healing was small (n=10). Moreover, in the RCT by Kobayashi et al., patients with Mayo 1 were not at higher risk of relapse than those with Mayo 0, but a trend for a lower risk was observed in patients in *histological* remission.[24] Thus, although it remains unclear whether we should aim for complete endoscopic or even histologic remission prior to anti-TNF withdrawal, our

study and the study by Kobayashi et al. consistently support the broader general concept: subclinical inflammation matters.

In patients with UC, we found that continuing mesalamine treatment may improve outcomes after withdrawal of anti-TNF treatment. If confirmed in (larger) future studies, starting or continuing mesalamine should be considered in this setting given the favorable safety profile of mesalamine. In patients with CD, continuation of the immunomodulator reduced the risk of relapse in prior studies[30], especially when 6-TGN levels were above 300 pmol/10^8 red blood cells.[23] This was not observed in our study, but the number of patients continuing immunomodulator therapy was small in our cohort. In prior studies, patients in remission with low anti-TNF trough levels had a lower risk of relapse after anti-TNF withdrawal, and the same trend was observed in our study.[26,31] In the study by Pierre et al., specific biomarkers were identified that predict a late relapse (after more than 6 months) following anti-TNF withdrawal. These biomarkers are thought to reflect fundamental disease characteristics rather than the presence or absence of inflammation.[32] Ideally, a panel of serum biomarkers (including the anti-TNF trough level and presence of anti-drug antibodies) should be developed to non-invasively predict which patients can safely de-escalate anti-TNF therapy.

Continuation of anti-TNF treatment

Although this thesis focuses mostly on the possibility of de-escalation of therapy, it is important to realize that most patients stay on anti-TNF maintenance therapy for many years. In **Chapter 5**, we studied reasons for anti-TNF withdrawal in routine clinical practice, among 708 patients on anti-TNF for at least four months between 2011-2019 in two large hospitals in The Netherlands. Loss of response was by far the most important reason to discontinue anti-TNF maintenance treatment. Loss of response could be attributed to the occurrence of anti-drug antibodies in 31% of cases, which was observed less often among patients with a concomitant immunomodulator (thiopurine or methotrexate) as expected.[19] Of note, 69% of the cases of loss of response could not be attributed to anti-drug antibodies. This phenomenon of sudden loss of response to anti-TNF without a pharmacokinetic explanation is poorly understood, and the immunologic mechanisms underlying this phenomenon require further elucidation.

We observed that the risk to benefit ratio of anti-TNF drugs in this setting depends on treatment duration. The risk of loss of response was much higher in the first two years of treatment (10-17% per patient-year, in line with prior studies[33,34]), than after more than two years of treatment (4.8-6.7% per patient-year). The risks of anti-TNF discontinuation due to side effects and anti-TNF dose escalations also decreased with longer treatment duration. This indicates that patients using long-term anti-TNF therapy represent a selected patient population with a relatively low risk of relapse, as long as the anti-TNF agent is continued. Whether these patients have a specific IBD phenotype that responds well to anti-

TNF treatment, or just a generally milder IBD phenotype remains unknown. Using clinical characteristics, no risk factors for loss of response were identified in our study, apart from UC (versus CD), and female sex and stricturing or penetrating disease in patients with CD. Future studies should assess whether immunologic or microbiotic characteristics can predict long-term response to anti-TNF therapy.

In the context of de-escalation of therapy, longer treatment duration does not protect against a relapse following anti-TNF withdrawal.[30] The favorable outcomes of continued treatment in **Chapter 5** may be interpreted as a strong rationale to continue anti-TNF treatment as long as possible. On the other hand, long-term users of anti-TNF therapy may represent a distinct population with anti-TNF responsive disease. Even after a relapse following anti-TNF withdrawal, these patients have a high likelihood to respond to anti-TNF reintroduction.[35] It is presently unclear if this short-term success translates in a long-term response as well.

Conclusion

The current paradigm of IBD treatment is to aim for remission based on objective assessment, rather than symptoms alone. Aiming for ambitious treatment targets such as endoscopic remission may decrease morbidity and IBD-related complications, but increases exposure to advanced therapies, including anti-TNF agents. Based on prior literature and the studies presented in this thesis, withdrawal of the immunomodulator from anti-TNF combination therapy in patients in remission to decrease treatment-related side effects is a feasible strategy. There is a rationale to consider withdrawal of anti-TNF treatment to decrease costs for society, to meet patient preferences and to reduce the risk of side effects. Only a highly selected patient population is eligible for withdrawal of anti-TNF, and endoscopic assessment of disease activity prior to anti-TNF withdrawal seems indispensable. Nevertheless, the risk of relapse remains high – although short-term outcomes following anti-TNF reintroduction are favorable. More research is needed to inform patients and clinicians on long-term outcomes of withdrawal versus continuation of anti-TNF. Future research should focus on biomarkers that predict the risk of relapse following anti-TNF withdrawal in a non-invasive manner. Until then, de-escalation of treatment requires careful case-by-case evaluation and shared-decision making.

SECTION II. Colitis-associated dysplasia and cancer

A rapidly changing landscape

The risk of colorectal cancer is increased in patients with IBD with colonic disease.[36–38] **Chapter 6** of this thesis presents a comprehensive clinical practice review of colitis-associated dysplasia and cancer. Similar to the *adenoma-carcinoma* sequence in sporadic colorectal cancer, colitis-associated cancer develops through several stages of precursor

lesions, including low-grade dysplasia (LGD), high-grade dysplasia (HGD) and ultimately colorectal cancer.[39] However, the tumorigenesis of colitis-associated cancer is distinct from sporadic colorectal cancer. Typically, in patients without IBD, DNA changes (e.g. APC mutations) occur that promote mucosal proliferation leading to an endoscopically visible polyp. Only later on, additional DNA changes (e.g. p53 mutations) occur focally within this polyp, causing chromosomal instability and eventually leading to colorectal cancer. In patients with IBD, chronic inflammation first leads to chromosomal instability (e.g. by causing p53 mutations) which may predispose large areas of the colonic mucosa to cancer development (a phenomenon termed *field cancerization*), despite a normal appearance on endoscopy and histology.[40] Next, additional mutations may lead to increased mucosal proliferation, leading to endoscopically visible lesions that ultimately give rise to colorectal cancer. The distinct biology of cancer development in IBD might explain the different phenotypic characteristics of dysplastic lesions in these patients, that are often flat and multifocal, difficult to detect endoscopically, and progress more rapidly to cancer.[39]

Guidelines recommend endoscopic surveillance in patients with IBD with colonic disease starting 8-10 years after the diagnosis of IBD, or immediately after the diagnosis of concomitant primary sclerosing cholangitis (PSC).[41–43] Endoscopic surveillance aims to mitigate the increased risk of colorectal cancer in IBD by identification and removal of dysplastic precursor lesions. Surveillance is technically challenging, as dysplastic lesions are subtle and may be obscured by the presence of inflammation or other abnormalities (post-inflammatory polyps, strictures), which hamper adequate assessment of the mucosa for endoscopists and pathologists. To increase the detection rate of dysplasia, adjunct techniques such as taking segmental random biopsies and use of chromo-endoscopy (contrast-enhancing dye sprays) are used.[44,45] Management of dysplasia depends on histological grading and possibility of radical endoscopic resection. In short, visible LGD can be managed with polypectomy (if possible) and yearly surveillance.[46] Until recently, subtotal or total colectomy has been the mainstay of management for non-resectable dysplasia, invisible dysplasia and HGD or cancer in patients with IBD, as the risk of future dysplasia or cancer is high due to field cancerization.[46] Currently however, a shift occurs towards endoscopic resection of complex lesions with advanced techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), followed by strict follow-up.[47]

Clinicians and researchers involved in the care for patients with IBD operate in a rapidly changing landscape. The risk of colorectal cancer appears to be decreasing in patients with IBD.[37,48] This may be attributed to improved medical management of inflammation, implementation of surveillance guidelines and advances in endoscopic techniques for mucosal visualization and resection of dysplasia. With modern high-definition endoscopes, it appears that dysplasia is more often visible,[46] and the added value of chromo-endoscopy[45,49] and taking random biopsies is low.[44] If confirmed by future studies, these time-consuming techniques may be reserved for patients at highest risk of dysplasia.

Currently, the surveillance interval for patients with IBD is either 5, 3 or 1 year(s), based on a risk-stratified approach in which the presence of one risk factor suffices to decrease the surveillance interval (see **Chapter 6**, Figure 1). Improved risk stratification may further increase the detection rate of dysplasia, while avoiding unnecessary procedures in patients at a relatively low risk for colorectal cancer. Specific risk factors were studied in **Chapter 7 and 8** of this thesis.

Risk factors for developing colorectal cancer

A recent meta-analysis studied risk factors for advanced colorectal neoplasia (ACRN: high-grade dysplasia and cancer) in patients with IBD. Thirteen risk factors were identified: extensive disease, LGD, PSC, UC (versus CD), post-inflammatory polyps (PIPs), family history of colorectal cancer, colonic strictures, histologic inflammation, age, colon segment resections, aneuploidy, male sex and any previous dysplasia. In addition, surveillance colonoscopies, smoking and use of thiopurines, statins and mesalamine were identified as protective factors for ACRN. Of note, extensive disease was the only factor for which strong evidence was available.

In **Chapter 7** of this thesis, we studied PIPs as a risk factor for dysplasia and cancer in patients with IBD undergoing surveillance in a retrospective cohort study. PIPs are polyp-like lesions that develop as a result of mucosal regeneration following severe inflammation. It is deemed unlikely that these lesions progress to dysplasia or cancer.[50] However, as PIPs are associated with severe prior inflammation, they may serve as a surrogate marker to predict the risk of colorectal cancer. Moreover, the presence of (fields of) PIPs may hamper adequate visualization of the colonic mucosa during surveillance. Prior case-control studies reported a higher prevalence of PIPs in patients with IBD with versus without colorectal cancer.[51–53] Current guidelines recommend to decrease the surveillance interval from 5 to 3 years if PIPs are present.[41,46]

In our large retrospective cohort study in **Chapter 7,** we confirmed that the presence of PIPs was associated with extensive disease and more severe histologic inflammation, while PIPs were less often encountered in patients with concomitant PSC. However, PIPs were not associated with an increased risk of ACRN or any colorectal neoplasia (low-grade dysplasia, high-grade dysplasia or colorectal cancer). Subsequently, de Jong et al. confirmed our findings in an independent Dutch IBD surveillance cohort.[54] In addition, in a retrospective study in the United Kingdom, PIPs were associated with a higher risk of colorectal neoplasia on univariable analysis, but this association disappeared after adjustment for confounders. An important confounder was the cumulative inflammatory burden, which was strongly predictive of colorectal neoplasia.[55] Thus, recent high-quality studies did not detect an independently increased risk of colorectal dysplasia or cancer in IBD patients with PIPs.

Based on the available literature, PIPs are not a reliable marker to predict the risk of colorectal cancer in patients with IBD. However, PIPs may still serve as a useful marker for clinicians, as they are associated with (prior) severe inflammation. All prior studies were retrospective and the density of PIPs could not be studied adequately. Most likely, patients without other risk factors for colorectal neoplasia and with few PIPs that still allow for adequate mucosal visualization during surveillance, do not benefit from increased surveillance. In contrast, dense fields of PIPs should remain a "red flag" for clinicians as these PIPs may obscure dysplasia and their presence should also prompt clinicians to evaluate other risk factors including the severity of (prior) inflammation. In patients with dense fields of PIPs, it should still be considered to decrease the surveillance interval.

Indefinite for dysplasia: explicit uncertainty

Detection of dysplasia is an important predictor of advanced dysplasia or colorectal cancer in patients with IBD. In the study by Choi et al., UC patients with a diagnosis of LGD had a risk of 3.9% per patient-year to develop ACRN.[56] The histopathologic diagnosis of LGD is not straightforward, as (regeneration of the mucosa after) inflammation may resemble dysplasia.[57] There is significant interobserver variability between pathologists in the diagnosis of dysplasia, and revision of the diagnosis by an expert panel of pathologists has been shown to increase the predictive potential for ACRN.[58] If no definite diagnosis of dysplasia can be established, pathologists may classify a sample as *indefinite for dysplasia* (IND). The progression rate of IND to ACRN is poorly understood.

In our retrospective study in **Chapter 8** we reported that a diagnosis of IND carries a higher risk for progression to ACRN than no dysplasia (3.1% versus 0.4% per patient-year), but lower than low-grade dysplasia (8.4% per patient-year), as expected. Of note, it was not known in our study if lesions were radically resected, which limits the interpretation of the progression rates to ACRN. Our results suggest that patients with IND, similar to LGD, benefit from increased surveillance. Results of additional analyses (with small sample size) suggested that a repeat colonoscopy after the diagnosis of IND distinguished patients at high versus low risk of ACRN. If this is confirmed in larger studies, it may (cautiously) be considered to increase the surveillance interval if the diagnosis of IND (or a higher grade of dysplasia) is not confirmed on subsequent procedures.

Importantly, IND was diagnosed more often in patients with concomitant PSC, extensive colitis and more severe inflammation, and IND lesions were less often visible. In this context, it is important to realize that in our cohort, patients were included from as far back as 2001. In the modern era with better medical therapies to control inflammation and a gradual practice shift towards only taking targeted biopsies (as even subtle lesions can be detected with high-definition endoscopes), it is likely that the incidence of IND will decrease over time. In addition, future research on aneuploidy and molecular biomarkers[59], may aid pathologists to make a final distinction between dysplastic versus non-dysplastic mucosa. With these

developments, IND may become a rare entity. Until then, increased surveillance is warranted in patients with IND.

Conclusion

The clinical and scientific field of colorectal cancer surveillance in patients with IBD is a rapidly changing landscape. The increased risk of colorectal cancer in patients with IBD is diminishing over time. This decrease may be attributed to improved medical management of inflammation with novel therapies and a paradigm shift towards a tight control strategy. In addition, implementation of surveillance programs and advances in endoscopic techniques contribute to a declining risk of colorectal cancer in IBD. In this thesis, we focused on risk-stratification of patients with IBD, which may aid to determine the surveillance interval. Specifically, PIPs do not independently increase the risk of colorectal dysplasia and cancer in patients with IBD, but the presence of PIPs should prompt a careful assessment of other risk factors and critical evaluation of the quality of surveillance in these patients. A diagnosis of IND is associated with an increased risk of colorectal dysplasia and cancer and warrants increased surveillance. Further research into histopathologic biomarkers may aid to clearly distinguish patients with versus without dysplasia. A detailed understanding of individual risk factors such as PIPs and IND is crucial, but eventually surveillance intervals should be tailored to the risk of colorectal cancer of the individual patient. To that end, future studies should focus on integrating multiple risk factors to develop a prediction model to enable individual risk assessment and determine a personalized surveillance interval.

Perspective

This thesis focused on the management of IBD beyond short-term remission induction. Taking a long-term perspective on this lifelong disease is, however, highly complex. Treatment risks and benefits are usually studied with different methods, complicating direct comparisons. The efficacy of a therapy is usually assessed in RCTs, with selected patient populations. This may not always be in line with the effectiveness of a treatment or strategy in routine clinical practice. In addition, rare side effects (e.g. the risk of lymphoma with anti-TNF combination therapy) are typically detected in large cohort studies, such as health insurance databases. Different perspectives, including the patient perspective, physician perspective and health-economic perspective may also yield conflicting views on the added value of a treatment or treatment strategy. This thesis modestly contributes to the body of literature on the long-term management of IBD, with studies on withdrawal as well as on continuation of anti-TNF treatment and immunomodulators, a cost-effectiveness study and studies on risk factors for colorectal cancer and dysplasia. With our review on IBD-related colorectal cancer, an effort was made to solve a part of the puzzle and identify pieces that are still missing.

The recent, rapid expansion of available medical therapies for IBD has stirred the field of IBD care and research. Key challenges for future research are to integrate data and to construct a coherent long-term perspective. New questions arise on how when to use these new therapies, in what order and in whom. To this end, the strategic randomized trials that are currently underway are valuable contributions. Prediction models may be useful to determine the individual risk of relapse after anti-TNF withdrawal and to personalize surveillance intervals for colorectal cancer.

While exciting research is ongoing, in every individual patient encounter, the challenge remains for physicians to combine all different perspectives and to construct the best possible picture despite the many pieces that are still missing.

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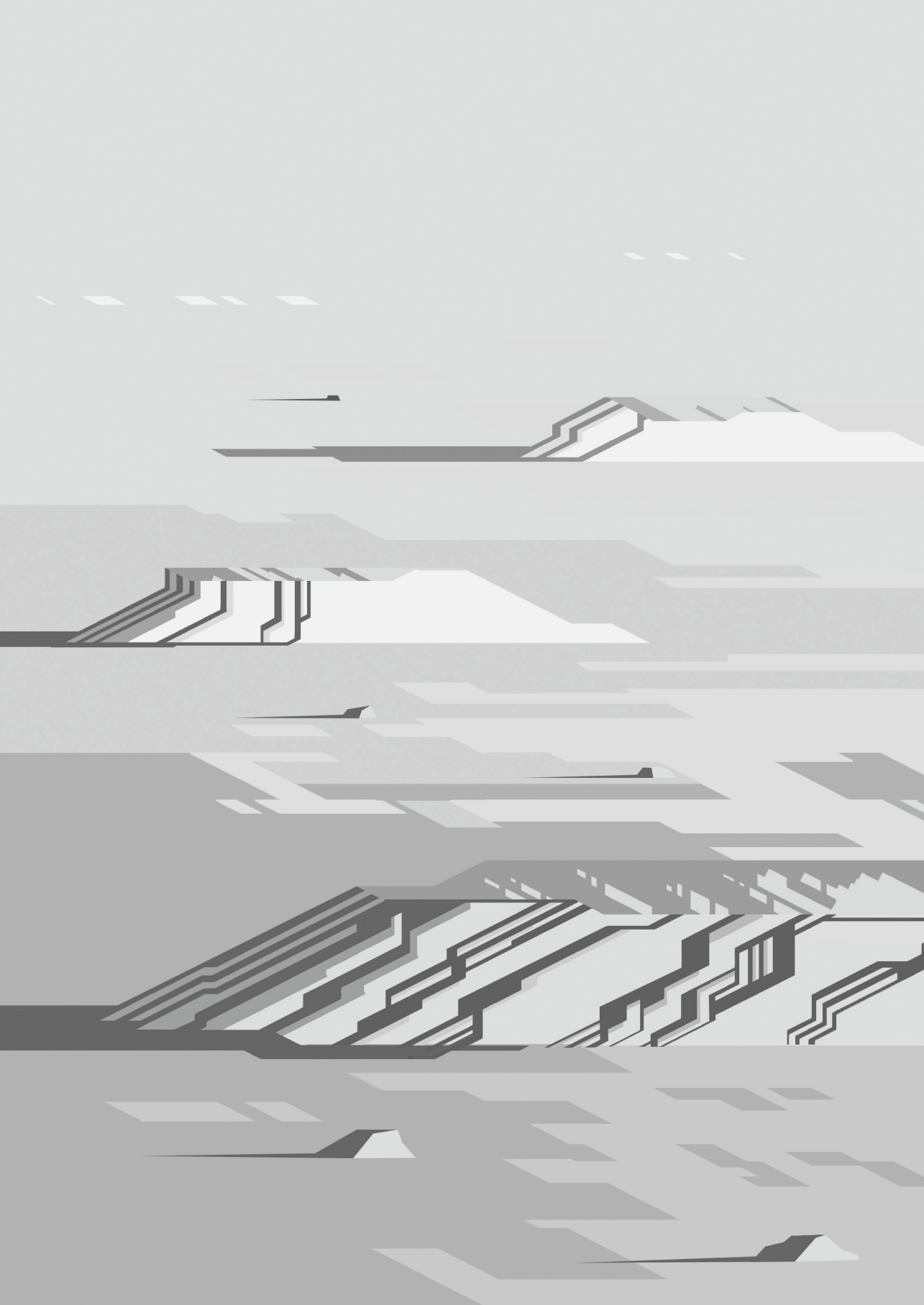


CHAPTER 10

Summary in Dutch

Nederlandstalige samenvatting

Behandeling van inflammatoire darmziekten: een langetermijnsperspectief

Introductie

De ziekte van Crohn en colitis ulcerosa zijn chronische, inflammatoire aandoeningen van het maag-darmstelsel. In het Engels worden deze ziekten samen *Inflammatory Bowel Disease* genoemd, en de afkorting *IBD* wordt ook in het Nederlands gebruikt. Het ziektebeloop van IBD is grillig en kent periodes van actieve ziekte, ook wel opvlammingen genoemd, afgewisseld met periodes zonder ziekte-activiteit, oftewel "remissie". Een opvlamming van IBD kan gepaard gaan met verscheidene symptomen, waaronder buikpijn, diarree, rectaal bloedverlies, gewichtsverlies en vermoeidheid. Bovendien leidt de terugkerende ontstekingsactiviteit in de darm tot chronische schade, waardoor bij de ziekte van Crohn vernauwingen, fistels en abcessen in de darm en bij de anus kunnen ontstaan, waarvoor niet zelden chirurgie noodzakelijk is. Bij colitis ulcerosa kan chronische ontsteking leiden tot motiliteitsstoornissen en verlittekening van de dikke darm. Patiënten met IBD waarbij de dikke darm langdurig en uitgebreid ontstoken is geweest, hebben bovendien een verhoogd risico op darmkanker, een gevreesde complicatie.

De behandeling van IBD richt zich allereerst op het onderdrukken van ontsteking en daarmee op het laten verdwijnen van de symptomen. Hiervoor worden immunosuppressiva gebruikt: medicijnen die het afweersysteem onderdrukken, waaronder prednison en immunomodulatoren (thiopurines en methotrexaat). In de afgelopen twee decennia zijn bovendien veel nieuwe medicijnen beschikbaar geworden, waaronder biologicals.

Biologicals zijn monoklonale antistoffen die periodiek via het infuus of subcutaan toegediend worden en een specifiek deel van het immuunsysteem remmen. De eerste biologicals voor de behandeling van de IBD waren "*anti-tumor necrosis factor-α*"-middelen (anti-TNF) waaronder infliximab en adalimumab. Inmiddels zijn ook andere biologicals (o.a. vedolizumab, ustekinumab) en nieuwe medicijnen in tabletvorm (o.a. tofacitinib, filgotinib) beschikbaar. Belangrijke bijwerkingen van immunosuppressiva zijn een verhoogd risico op (ernstige) infecties en een verhoogd risico op verschillende vormen van kanker. Zo is bij anti-TNF medicatie het risico op melanoom verhoogd, bij thiopurines zijn het risico op andere vormen van huidkanker (plaveiselcelcarcinoom en basaalcelcarcinoom) en het risico op lymfeklierkanker verhoogd. De combinatie van anti-TNF medicatie met een immunomodulator is effectiever om remissie te bereiken dan anti-TNF monotherapie, met name voor infliximab in combinatie met azathioprine. Helaas is echter ook het risico op infecties en maligniteiten (met name het risico op lymfeklierkanker) hoger bij gelijktijdig gebruik van deze middelen.

Niet alleen zijn er nieuwe medicijnen beschikbaar voor de behandeling van IBD, er is ook een verschuiving gaande in het vakgebied om ontsteking niet alleen te behandelen totdat de patiënt geen symptomen meer ervaart, maar om ook objectief vast te stellen dat er geen asymptomatische ontsteking meer is op basis van ontstekingswaarden in bloed (CRP) en ontlasting (fecaal calprotectine), of zelfs endoscopisch middels een kijkonderzoek van de darm.

Om opvlammingen, en daarmee uiteindelijk ook chronische schade, te voorkomen wordt met regelmaat gebruik gemaakt van langdurige onderhoudsbehandeling met immunosuppressiva. Hierbij is het van belang de bijwerkingen van de behandeling af te wegen tegen de effectiviteit. Vanuit maatschappelijk perspectief moet bovendien in acht genomen worden dat veelvuldig gebruik van dure, nieuwe medicatie leidt tot stijgende zorgkosten.

Patiënten met IBD waarbij de dikke darm uitgebreid is aangedaan komen in aanmerking voor een screeningsprogramma voor darmkanker op het moment dat er meer dan 8 jaar ziekteduur is. Afhankelijk van risicofactoren wordt patiënten geadviseerd eens per jaar, per drie jaar of per vijf jaar een coloscopie (kijkonderzoek van de dikke darm) te ondergaan. Patiënten met een bijkomende auto-immuun galwegonsteking (primair scleroserende cholangitis, PSC) hebben een sterk verhoogd risico op darmkanker en ondergaan direct vanaf de diagnose jaarlijks een coloscopie. Het doel is om afwijkend darmslijmvlies (dysplasie) op te sporen en te verwijderen, om te voorkomen dat dit zich uiteindelijk tot darmkanker ontwikkelt. Bij IBD zijn deze laesies vaak geen gesteelde poliepen, maar vlakke laesies die lastig te herkennen en te reseceren zijn. In de afgelopen decennia hebben grote ontwikkelingen plaatsgevonden met betrekking tot de endoscopische technieken voor het visualiseren van het darmslijmvlies en het reseceren van dysplastische laesies. Het risico op darmkanker bij IBD lijkt zelfs af te nemen, waarschijnlijk ten gevolge van verbeterde screening in combinatie met verbetering van de medicamenteuze behandeling waardoor de cumulatieve schade aan de darm ten gevolge van ontsteking afneemt. De uitdaging voor het screeningsprogramma bij IBD is om de onderzoeken zo gericht mogelijk in te zetten om darmkanker te voorkomen, maar patiënten zo min mogelijk te belasten.

Dit proefschrift richt zich op de lange termijn behandeling van IBD. In deel I van dit proefschrift worden de voor- en nadelen van langdurige behandeling met anti-TNF medicatie met of zonder immunomodulatoren nader bestudeerd, en wordt de mogelijkheid tot het staken van medicatie besproken. Deel II van dit proefschrift richt zich op het screeningsprogramma voor darmkanker bij IBD en onderzoekt de toegevoegde waarde van specifieke risicofactoren voor risico-stratificatie.

Deel I. Onderhoudstherapie met anti-TNF medicatie en de-escalatie van therapie
De zorgkosten van onderhoudsbehandeling met anti-TNF zijn hoog, maar het risico op een opvlamming binnen een jaar na staken is groot. Het doel van **hoofdstuk 2** was om

te onderzoeken of het staken van anti-TNF medicatie kosten-effectief is ten opzichte van het continueren van de behandeling bij patiënten met colitis ulcerosa die tenminste 1 jaar in remissie zijn. Met behulp van eerdere literatuur en een expert-panel werd een zogenaamd Markov model ontworpen, vanuit het perspectief van de zorgverlener. In dit model werd op een termijn van vijf jaar, in driemaandelijkse cycli, geschat welke behandeling patiënten zouden krijgen na het staken versus continueren van anti-TNF medicatie, met welke zorgkosten dit gepaard zou gaan en wat de kwaliteit van leven van de patiënten zou zijn. Na vijf jaar resulteerde het staken van anti-TNF in lagere zorgkosten (totaal -€10,781 per patiënt), met slechts een geringe afname in kwaliteit van leven (-0.04 *quality-adjusted lifeyear*). Doorgaan met de behandeling is daarmee niet kosten-effectief (€300,390 per *quality-adjusted lifeyear,* waarbij de afkapwaarde voor kosten-effectiviteit doorgaans op €80,000 wordt gesteld) De belangrijkste determinanten van de kosten-effectiviteit waren het percentage opvlammingen na staken en de prijs van adalimumab en infliximab. Belangrijke beperkingen van dit onderzoek zijn dat het een model betreft en geen empirische data, en dat indirecte kosten (arbeidsproductiviteit) niet geschat konden worden. Concluderend is er vanuit maatschappelijk perspectief een rationale om anti-TNF medicatie te staken bij patiënten met colitis ulcerosa na 1 jaar remissie. De kosten-effectiviteit kan verder verbeterd worden indien er effectieve risico-stratificatie plaats zou kunnen vinden.

Hoofdstuk 3 beschrijft de resultaten van de AWARE studie: een multicenter prospectieve studie naar het staken van anti-TNF medicatie bij patiënten met IBD die tenminste zes maanden in klinische en endoscopische remissie zijn zonder het gebruik van corticosteroïden (prednison). Het doel van de studie was om het percentage opvlammingen te bepalen en voorspellers te identificeren in een cohort met een verwacht laag risico op een opvlamming na het staken van anti-TNF. Van de 81 deelnemers, was er bij 40 (49%) van de patiënten sprake van een opvlamming na een mediane follow-up van 2 jaar. Complete endoscopische heling voor het staken van de anti-TNF medicatie, was geassocieerd met een lager risico op een opvlamming ten opzichte van partiële endoscopische heling (SES-CD score 3-4, Mayo score 1). Bij partiële endoscopische heling is er sprake van zeer milde ontsteking van de darm die doorgaans als irrelevant wordt geduid indien er geen sprake is van symptomen. Het starten of continueren van mesalazine was geassocieerd met een lager risico op een opvlamming bij patiënten met colitis ulcerosa. Dertig patiënten waren genoodzaakt anti-TNF medicatie te herstarten, waarbij 73% drie maanden daarna in klinische remissie was. Concluderend was er ook in dit cohort sprake van een hoog risico op een opvlamming na het staken van de onderhoudsbehandeling met anti-TNF. De endoscopische uitgangssituatie en gebruik van mesalazine waren gerelateerd aan het risico op een opvlamming.

In **hoofdstuk 4 en 5** worden de resultaten van een retrospectieve studie naar IBD patiënten die tenminste 4 maanden anti-TNF medicatie gebruikten volgens de reguliere klinische praktijk. Voor deze studie werden gegevens uit de periode 2011-2019 verzameld in twee grote Nederlandse ziekenhuizen. Indien er gestart wordt met anti-TNF medicatie in

combinatie met een immunomodulator, wordt gedurende de onderhoudsbehandeling de immunomodulator vaak gestaakt om het risico op bijwerkingen te verminderen. In **hoofdstuk 4** worden 296 versus 318 behandelepisodes onderzocht waarin de immunomodulator werd gestopt versus gecontinueerd. Er werd geen verschil waargenomen in het falen van anti-TNF therapie. Wel vormden patiënten vaker antistoffen tegen de anti-TNF therapie en waren infliximab dalspiegels lager na het staken van de immunomodulator. Klinische remissie en hogere infliximab dalspiegels voor het staken van de immunomodulator waren geassocieerd met een lager risico op het falen van de anti-TNF therapie. Het risico op antistofvorming was lager bij patiënten die langer met combinatietherapie behandeld waren, en/of hogere infliximab dalspiegels hadden voor het staken van de immunomodulator. Een belangrijke beperking is dat dit geen gerandomiseerde studie betreft.

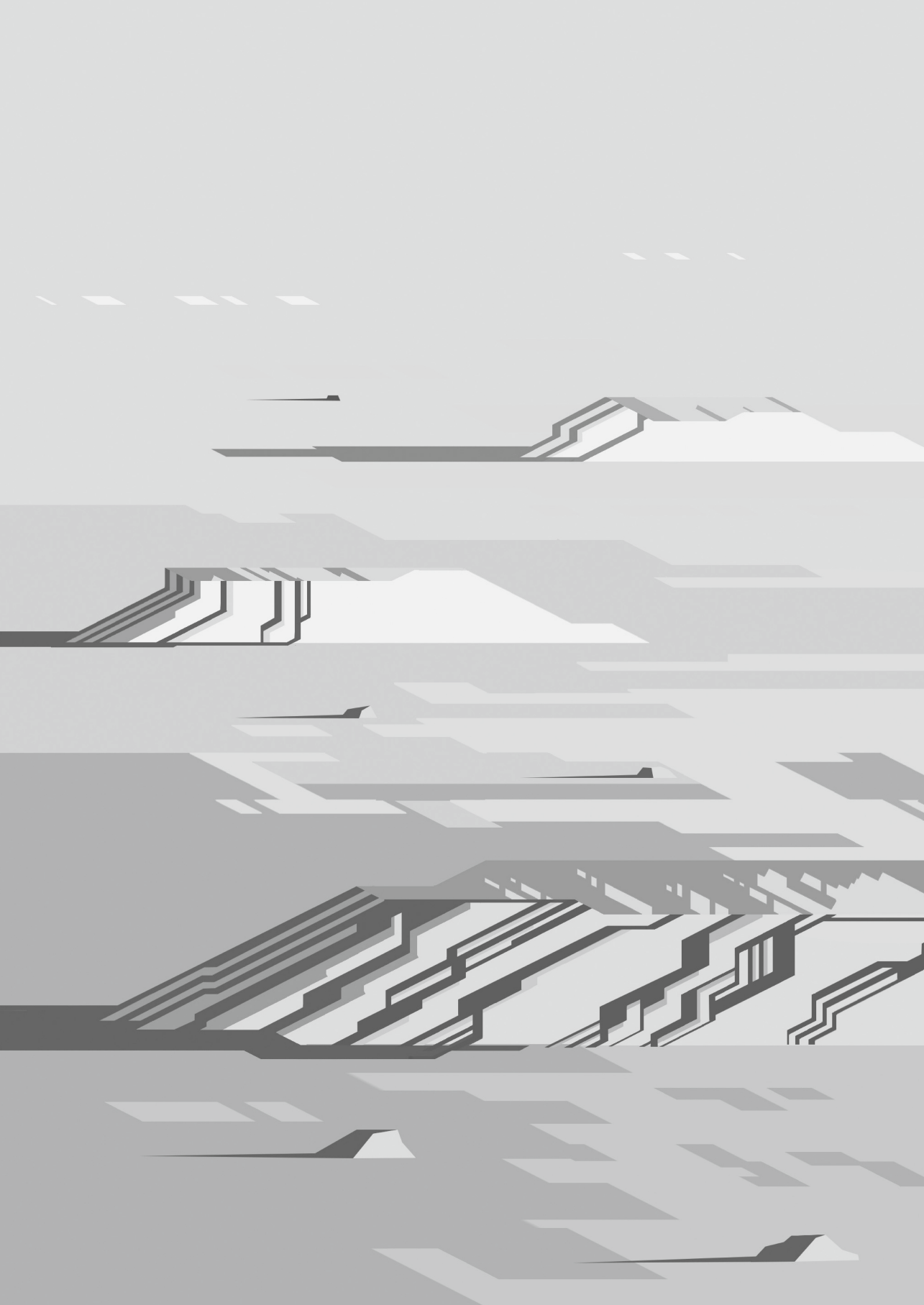
Veel eerder onderzoek richt zich op uitkomsten in het eerste jaar van anti-TNF therapie. In **Hoofdstuk 5** wordt onderzocht hoe de kans op therapiefalen, bijwerkingen en antistofvorming veranderen bij langere behandelduur. De incidentie van therapiefalen neemt sterk af, van 17.2% naar 4.8% per patiënt-jaar in het eerste jaar versus na vier jaar behandeling. Ook de noodzaak tot dosis-verhoging en therapiefalen door bijwerkingen en/of antistofvorming namen af over de tijd. Het percentage patiënten dat uit eigen beweging stopte met medicatie bleef gelijk, en geplande stoppogingen wegens stabiele remissie namen juist toe. Concluderend lijkt er met langere behandelduur sprake te zijn van selectie van patiënten die meer profijt hebben van de behandeling en deze goed tolereren. Of dit een selectie is van patiënten met een milder fenotype van de IBD of patiënten die specifiek baat hebben bij anti-TNF medicatie is onzeker.

Deel II. Risico op darmkanker bij patiënten met IBD

Hoofdstuk 6 is een review over het risico op darmkanker bij patiënten met IBD. Er wordt besproken welke gelijkenissen en verschillen er zijn in de pathogenese van colitis-geassocieerd darmkanker versus sporadisch darmkanker. De incidentie van darmkanker bij IBD is ongeveer 0.1% per patiënt-jaar, maar in de populatie die voor screening in aanmerking komt circa 0.3-0.5% per patiënt-jaar. Het risico lijkt wel af te nemen over te tijd, waarschijnlijk door betere behandeling en screening. Voorts worden risicofactoren en de risicostratificatie van verschillende richtlijnen besproken. Door verbeterende endoscopische technieken voor visualisatie van het darmslijmvlies kan de screeningsprocedure mogelijk vereenvoudigd worden: de toegevoegde waarde van willekeurige biopten van gezond-ogend slijmvlies en het sprayen van contrast-verbeterende kleurstof staan ter discussie. Er is een verschuiving gaande van chirurgische behandeling naar endoscopische resectie van dysplastische laesies, maar de lange termijn veiligheid moet verder worden onderzocht. Er is nog onvoldoende bewijs dat het zinvol is om specifieke medicatie voor te schrijven alleen om het risico op darmkanker bij IBD te verminderen.

Hoofdstuk 7 en 8 betreffen retrospectieve studies over patiënten met IBD die periodieke screening ondergaan voor darmkanker in verschillende ziekenhuizen in Nederland en/of een groot ziekenhuis in de Verenigde Staten. **Hoofdstuk 7** richt is op de voorspellende waarde van post-inflammatoire poliepen (PIPs) met betrekking tot het risico op darmkanker of hooggradige dysplasie. Deze PIPs ontstaan in het genezingsproces na ernstige ontsteking en/of diepe zweren. Volgens de huidige Europese richtlijnen verschuift het screeningsinterval van 5 naar 3 jaar, wanneer PIPs worden aangetroffen (in afwezigheid van andere risicofactoren). PIPs werden beschreven bij 462 van de 1582 onderzochte patiënten in hoofdstuk 7, en waren geassocieerd met ernstigere ontsteking en meer uitgebreide ontsteking. Bij patiënten met een bijkomende diagnose PSC kwamen PIPs minder vaak voor. PIPs waren geen onafhankelijke voorspeller voor het risico op darmkanker en (hooggradige) dysplasie. Wel werd vaker een colectomie verricht bij patiënten met PIPs, met name wegens ernstige ontsteking. Een belangrijke kanttekening is dat het niet mogelijk was om in het volledige cohort een onderscheid te maken in hoe uitgebreid PIPs aanwezig waren en of dit het visualiseren van het darmslijmvlies tijdens de screening belemmerde.

De aanwezigheid van laaggradige dysplasie is een belangrijke voorspeller voor het risico op darmkanker bij patiënten met IBD en een reden om tenminste vaker screening te verrichten. Soms kan de patholoog echter niet duidelijk onderscheiden of laaggradige dysplasie aanwezig is, bijvoorbeeld door aanwezigheid van ontsteking in het preparaat. In een dergelijk geval kan de diagnose "*indefinite for dypslasia"* (IND) gesteld worden. In het cohort van 492 patiënten uit de Verenigde Staten in **hoofdstuk 8**, werd bij 53 patiënten de diagnose IND gesteld. Het risico op kanker en hooggradige dysplasie was significant hoger dan bij afwezigheid van dysplasie, maar significant lager ten opzicht van laaggradige dysplasie. Opvallend was dat IND vaak endoscopisch onzichtbaar was (i.e. gediagnosticeerd door willekeurig biopteren), en indien de diagnose niet werd bevestigd bij de eerstvolgende endoscopie, het risico op hooggradige dysplasie of kanker laag was. Om dit laatste te bevestigen is meer onderzoek nodig. De bevindingen van **hoofdstuk 7 en 8** kunnen mogelijk in de toekomst geïntegreerd worden in een voorspelmodel dat het individuele risico op darmkanker schat bij patiënten met IBD.



APPENDICES

Appendix B. List of publications relevant to this thesis

In 2016 nam ik als student geneeskunde contact op met een zekere maag-darm-leverarts in Utrecht, die een begaafd spreker is en kort daarvoor een college had gegeven over inflammatoire darmziekten. Nu, zeven jaar later, ben ik zelf in opleiding tot maag-darm-leverarts en heeft het verzoek uit 2016 voor een wetenschappelijke stage zich ontwikkeld tot het proefschrift dat voor u ligt. Dit proefschrift is een team effort, het resultaat van jarenlange samenwerking, iets waar velen een bijdrage aan geleverd hebben. Ik ben iedereen dankbaar die heeft meegewerkt aan de totstandkoming van dit proefschrift, op wetenschappelijk, organisatorisch of vriendschappelijk vlak. Ik bedank in het bijzonder alle patiënten die hebben deelgenomen aan het onderzoek dat ten grondslag ligt aan dit proefschrift. De volgende personen wil ik specifiek noemen:

Prof. dr. B. Oldenburg, beste Bas, dank voor al het vertrouwen. Je hebt me bijzonder veel vrijheid gegeven om eigen onderzoek te ontwerpen gedurende mijn promotietraject. Je bent ontzettend nauw betrokken bij je promovendi. Onze wekelijkse besprekingen werden regelmatig een kleine oratie van jouw kant. Als dit uiteindelijk een concreet onderzoeksplan werd, gaf je me vervolgens als genereuze mentor het gevoel gaf dat het mijn initiatief was. Jouw enthousiasme en optimisme zijn oneindig en aanstekelijk, en hiermee heb je mij feilloos door alle lastige logistiek en bureaucratie gecoacht.

Dr. B. Jharap, beste Bindia, wij delen een sterke interesse in onderzoek dat direct aansluit op de dagelijkse klinische praktijk. Ik bewonder hoe je je hectische klinische baan combineert met wetenschap. Jouw vlijmscherpe kritische blik heeft menig manuscript naar een hoger niveau getild. Met de AWARE studie hebben we samen echt een mooie regionale samenwerking opgezet, wat natuurlijk startte in jouw ziekenhuis, het Meander Medisch Centrum in Amersfoort. Enorm leuk om je daar nu ook als clinicus in actie te zien!

Prof. dr. S. Itzkowitz, dear Steve, thanks for the wonderful supervision at Mount Sinai Hospital. In this place with endless research opportunities, you made sure that I was able to focus. Meanwhile, you ensured that I didn't miss out on the jazz scene in New York City! You're a great narrator, critical academic and kind mentor all at once. I'm glad to have you in my supervision committee, things have come full circle.

Dr. S.C. Shah, dear Shailja, you are truly inspirational. Despite a career switch from IBD research to gastric cancer research, you continued to offer excellent remote supervision from Nashville and later on from San Diego. Not to mention your brief visit to Amsterdam after running the marathon in Paris! The world wonders if you ever sleep.

Dr. H.H. Fidder, beste Herma, beste buurvrouw, samen met Hans-Paul hebben we een aantal mooie projecten opgestart. Van jouw mentaliteit om de professionele zaken kort en

bondig te houden zodat iedereen op tijd naar de borrel kan (overigens zonder enig verlies van kwaliteit), kan menigeen wat leren!

Veel dank aan alle artsen, onderzoekers en verpleegkundigen die aan de AWARE studie hebben bijgedragen. De bereidheid om samen te werken aan dit project was onverwacht groot. Velen van jullie hebben dit alles in eigen tijd gedaan naast alle dagelijkse hectiek, puur uit motivatie om iets bij te dragen aan het vakgebied. Ik heb hier veel bewondering voor. In het bijzonder dank aan **Edo Savelkoul**, wij hebben samen behoorlijk wat werk verzet om de studie draaiende te houden – dat schept een band.

De volgende instanties wil ik zeer hartelijk bedanken voor een financiële bijdrage aan dit proefschrift: ChipSoft, Dr. Falk Pharma Benelux B.V., Ferring B.V., het programma "Infection and Immunity" van de graduate school of lifes sciences van het UMC Utrecht, de Nederlandse Vereniging voor Gastroenterologie, Stichting Fonds Ebe Brander and Teva Nederland B.V. Voor het mogelijk maken van de AWARE studie bedank ik het Innovatiefonds Zorgverzekeraars. Voor de bijdragen aan mijn verblijf aan Mount Sinai Hospital te New York bedank ik de Nijbakker-Morra Stichting, het K.F. Hein Fonds, het Holland Scholarship van het Ministerie OCW en de Stichting Fundatie van de Vrijvrouwe van Renswoude te 's-Gravenhage.

Thomas van Dun, ik vind het een eer dat je de cover van mijn proefschrift hebt ontworpen. Ik bewonder je artistieke carrière als componist en schilder en kijk uit naar alles wat je nog gaat maken.

Lieve collega's van de "Suite" (zoals we ons gezamenlijke hok in het UMC Utrecht noemen), **Anouk O, Anouk W, Cas, Charlotte, Eelco, Hans-Paul, Ilse, Janine, Jonas, Kim, Krijn, Lisa, Lisanne, Maartje, Jonas, Koen, Veronique, Victor, Yorick** en tegenwoordig ook **Laura** en **Rixta**, jullie zijn veel meer vrienden dan collega's. Dankzij jullie was mijn promotietraject een feestelijke aaneenschakeling van traktaties, borrels en geslaagde weekendjes weg. Ook waren er vele sportieve hoogtepunten: de Gastrolympics, de regen trotseren op de fiets tijdens de Zuiderzee klassieker en het verstoren van de dagelijks rust in het UMC Utrecht met luidruchtig, fanatiek tafelvoetbal. Hoe leuk om een deel van jullie nu weer tegen te komen in de kliniek of bij onderwijs! **Hans-Paul**, wij vullen elkaar supergoed aan als onderzoekers, in de kliniek en bovenal als vrienden. Op sommige vlakken heel anders (laten we zeggen dat je nét iets meer stoïcijns bent dan ik), dan weer erg hetzelfde (sportiviteit). Ik kijk uit naar nog vele ingewikkelde bordspellen en ben blij dat je mijn paranimf bent.

Lieve vrienden van mijn geneeskunde-opleiding SUMMA, lieve **Dorine, Elise, Floortje, Gautam, Simone, Siri** en **Timon**, onze gezamenlijke opleiding is een sociale snelkookpan geweest, met natuurlijk als hoogtepunt onze coschappen in Apeldoorn. Daarnaast ben ik de halve wereld over geweest om jullie tegen te komen in Maleisië, Singapore, Zwitserland, Oxford, Londen, Cuba, New York of Chili. Ik vrees dat ik sindsdien nooit meer van jullie afkom,

en jullie niet van mij. We kunnen met elkaar zoveel delen over onze carrières omdat we elkaar hierin volledig begrijpen, maar tegelijk maken we heel andere keuzes en hebben jullie allemaal een zoveel bredere blik dan alleen Geneeskunde met een hoofdletter. **Simone**, onze promoties liepen behoorlijk synchroon en we hebben ongeveer ons hele proefschrift inclusief alle logistieke lastigheden met elkaar besproken – bij voorkeur in het bijzijn van Gautam die ons veel te serieus vindt. Veel dank dat je dit met me wilt afsluiten als mijn paranimf.

Lieve **Robin, Nienke, Aram, Laura, Romy, Annemiek, Olga, Pim, Lieke** en **Lotte**, het maakt niet uit waar ik qua werk mee bezig ben: jullie zijn er altijd! Ik bedankt jullie vooral voor alle momenten die zo min mogelijk met dit proefschrift te maken hebben. Al onze etentjes en culturele of sportieve uitstapjes die het leven leuker maken, zowel voor- tijdens als na mijn promotietraject!

Aan mijn ouders, jullie zijn harde werkers en jullie zijn de nodige buitenlandse avonturen aangegaan. Ik bedank jullie voor de stimulerende omgeving waarin ik opgegroeid ben. Het is niet moeilijk om te zien van wie ik mijn ambitie geërfd heb. Ik kan nog altijd op jullie terugvallen. Lieve **Karim**, ik word nog regelmatig herkend als “het broertje van” of zelfs met jouw naam aangesproken – maar het is een groot compliment. We vullen elkaar goed aan met dezelfde interesses, maar toch heel verschillende aanpak.

Lieve **Jean-Luc**, je bent onmisbaar. Tijdens mijn promotietraject ben je altijd als eerste aan de beurt geweest om mijn eindeloze monologen aan te horen en je hebt het dapper doorstaan. Dank voor al je steun en je eindeloze geduld. We hebben inmiddels de nodige ervaring opgebouwd met dagenlange tochten in de bergen, en ik kijk uit naar alle gezamenlijke expedities die nog gaan volgen, te beginnen met Nieuw-Zeeland!

Appendix B. List of publications relevant to this thesis

Mahmoud R, van Lieshout C, Frederix GWJ et al. Continuation of anti-TNF in patients with ulcerative colitis in remission is not cost-effective compared with treatment withdrawal: a Markov model. *Journal of Crohn's and Colitis* 2021 May 4;15(5):709-718.

Mahmoud R, Savelkoul EHJ, Mares W et al. Complete endoscopic healing is associated with a lower relapse risk after anti-TNF withdrawal in inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2022 Aug 31;S1542-3565(22)00820-5.

Mahmoud R, Schultheiss JPD, Louwers JM et al. Immunomodulator withdrawal from anti-TNF therapy is not associated with loss of response in inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2022 Nov;20(11):2577-2587.

Schultheiss JPD, **Mahmoud R**, Louwers JM et al. Loss-of-response to anti-TNFα depends on treatment duration in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2021 Nov;54(10):1298-1308.

Wijnands AM, **Mahmoud R**, Lutgens WMD, Oldenburg B. Surveillance and management of colorectal dysplasia and cancer in inflammatory bowel disease: current practice and future perspectives. *Eur J Intern Med*. 2021 Nov;93:35-41.

Mahmoud R, Shah SC, ten Hove JR, et al. No Association Between Pseudopolyps and Colorectal Neoplasia in Patients With Inflammatory Bowel Diseases. Gastroenterology. 2019 Apr;156(5):1333-1344.

Mahmoud R, Shah SC, Torres J, et al. Association Between Indefinite Dysplasia and Advanced Neoplasia in Patients With Inflammatory Bowel Diseases Undergoing Surveillance. *Clin Gastroenterol Hepatol*. 2020 Jun;18(7):1518-1527.

Appendix C. About the author

Remi Mahmoud was born on July 14th 1992 in Arnhem, the Netherlands. In 2010 he graduated from the "Willem Lodewijk Gymnasium" in Groningen and started a double bachelor's degree at Utrecht University in Liberal Arts and Sciences and Biomedical Sciences. After his graduation in 2014, he started his medical training in the "Selective Utrecht Medical Master (SUMMA)" master's program at the University Medical Center Utrecht (UMCU). In 2017, he visited the Mount Sinai Hospital (MSH) in New York City, USA, during six months and wrote his master's thesis on risk factors for colorectal neoplasia in patients with inflammatory bowel disease, under supervision of prof. Steven Itzkowitz (MSH) and prof.dr. Bas Oldenburg (UMCU). After graduating *cum laude* from SUMMA in 2018, he started his PhD at the Department of Gastroenterology and Hepatology of the UMCU, under supervision of prof.dr. Bas Oldenburg and dr. Bindia Jharap (Gastroenterologist at Meander Medical Center, Amersfoort). As part of his training in gastroenterology, Remi is currently working as a resident at the Department of Internal Medicine at the Meander Medical Center, Amersfoort, The Netherlands.