Received: 29 March 2019 | Accepted: 17 April 2019

DOI: 10.1002/ygh2.337

GastroHep WILEY

De-escalating medical therapy in Crohn's disease patients who are in deep remission: A RAND appropriateness panel

Miles P. Sparrow[1,2] | Gil Y. Melmed[1,3] | Shane Devlin[1,4] | Patricia Kozuch[1,5] | Laura Raffals[1,6] | Edward V. Loftus Jr[6] | David T. Rubin[7] | Brennan Spiegel[3] | Leonard Baidoo[1,8] | Brian Bressler[1,9] | Adam Cheifetz[1,10] | Peter Irving[1,11] | Jennifer Jones[1,12] | Gilaad G. Kaplan[1,4] | Fernando Velayos[1,13] | Corey A. Siegel[1,14]

[1]The BRIDGe Group

[2]The Alfred Hospital, Melbourne, Victoria, Australia

[3]Cedars-Sinai Medical Center, Los Angeles, California

[4]University of Calgary, Calgary, Alberta, Canada

[5]Jefferson University, Philadelphia, Pennsylvania

[6]Mayo Clinic, Rochester, Minnesota

[7]University of Chicago Medicine, Chicago, Illinois

[8]Northwestern Hospital, Chicago, Illinois

[9]University of British Columbia, Vancouver, British Columbia, Canada

[10]Beth Israel Deaconess Medical Center, Boston, Massachusetts

[11]Guy's and St. Thomas' Hospitals, London, UK

[12]Dalhousie University, Halifax, Nova Scotia, Canada

[13]Kaiser Permanente, San Francisco, California

[14]Dartmouth-Hitchcock IBD Center, Lebanon, New Hampshire

Correspondence
Miles P. Sparrow, MBBS, FRACP, Clinical Head, Inflammatory Bowel Disease Unit, Department of Gastroenterology, Alfred Health, 99 Commercial Road, Melbourne, 3004 Australia.
Email: m.sparrow@alfred.org.au

Summary

Background: Deep remission is a treatment goal for patients with Crohn's disease, after which de-escalation of medical therapy may be considered. However, applicability of available study data to real-world clinical practice can be challenging.

Aim: We evaluated the appropriateness of de-escalating immunomodulator or anti-tumour necrosis factor therapy in Crohn's disease patients in deep remission.

Methods: A literature review was presented to a panel of international experts in Crohn's disease. Appropriateness of de-escalation in patients in deep remission for at least 6 months was considered in 240 scenarios across five chapters. Using a modified Delphi method, panel members rated appropriateness of de-escalation in each scenario via a web-based survey, then met to discuss the topic and re-rated the scenarios. Scenarios with disagreement were rated as uncertain.

Results: De-escalation was rated appropriate in only 32/240 scenarios (13.3%), including 19 of elderly patients on combination therapy. De-escalation was rated inappropriate in 59/240 scenarios (24.6%), including 22 of patients on monotherapy and 35 of patients on combination therapy stopping anti-tumour necrosis factor therapy. More than 60% of scenarios (149/240) were rated uncertain, including 42 of patients with complicated disease on combination therapy stopping or dose-reducing immunomodulators.

Conclusions: Discontinuing anti-tumour necrosis factor or immunomodulator therapy was largely not recommended, except in scenarios of elderly patients with uncomplicated CD or those on combination therapy stopping or dose-reducing immunomodulators. As nearly two-thirds of scenarios were rated uncertain, additional data are needed to better inform clinicians regarding the benefits and risks of de-escalating medical therapy in Crohn's disease.

1 | INTRODUCTION

Deep remission is a treatment goal for patients with Crohn's disease (CD) and marks a point at which de-escalation of anti-tumour necrosis factor (TNF) and immunomodulator (IM) therapy may be considered. Ideally, de-escalation would occur in those at highest risk of potential complications such as infection or malignancy, or in those at lowest risk of relapse after therapy is discontinued. Although de-escalation studies exist, the extrapolation and application of such data to common and complex clinical scenarios that reflect the spectrum of age, gender, therapies tried and severity of CD encountered by clinicians remains elusive. De-escalation studies to date have evaluated outcomes in patients treated with anti-TNF therapy in combination with IM therapy who discontinue the anti-TNF or IM,[1-7] as well as in patients on anti-TNF or IM monotherapy who are withdrawn from therapy.[2,8-13] Meta-analyses of de-escalation strategies demonstrate a relapse rate of approximately 50% at 2 years in patients treated with combination therapy who discontinued the anti-TNF,[1-3] and a similar rate is seen in those who discontinue anti-TNF monotherapy.[1] Relapse rates among those who discontinue the IM after combination therapy are slightly higher at 55%-60%, and those who discontinue IM monotherapy show relapse rates at 2 years up to 70%.[1] These studies showed that re-treatment with the same agent is successful in achieving remission in most, but not all, patients.[1-3]

Extrapolating from these data, clinical and biochemical factors associated with the risk of relapse have been identified,[1,14-16] and algorithms for de-escalation have been proposed.[17] However, prospective trials of anti-TNF/IM withdrawal in patients on combination therapy are still ongoing,[18,19] and prospective trials of IM monotherapy withdrawal to date have assessed only thiopurines,[10-13] potentially limiting applicability of study results to real-world clinical practice where both thiopurines and methotrexate are used.

We sought to address this deficiency in the area of de-escalation of anti-TNF and IM therapy in patients with CD who achieve deep remission. We used the RAND/University of California Los Angeles (UCLA) Appropriateness Method to assess expert opinion in the context of the available literature.[20] This evidence-based process is designed to determine appropriate use of medical diagnostics and therapeutics when high-quality, head-to-head evidence is lacking, making it ideal for considering risks and benefits of de-escalating medical therapy given the paucity of direct, prospective evidence on outcomes in different patient populations. Our aim was to provide guidance for clinicians on the appropriateness of de-escalating anti-TNF or IM therapy in patients with CD who are in deep remission.

2 | MATERIALS AND METHODS

2.1 | Study overview

The RAND/UCLA Appropriateness Method uses an iterative, modified Delphi panel approach to weigh the benefits and harms of medical or surgical interventions.[20] After reviewing the literature, each member of the panel anonymously and independently rates the appropriateness of interventions in the proposed clinical scenarios based on both evidence and expert opinion. No attempt is made to achieve consensus. Instead, panel members anonymously rate the scenarios a second time after participating in a moderated, in-person meeting to discuss areas of disagreement. Appropriateness is rated on a scale of 1-9, such that interventions rated 1-3 are considered inappropriate, 4-5 are uncertain and 7-9 are appropriate.

2.2 | Literature review

In December 2016, four panel members (MPS, SD, PK and LR) summarised available published literature on de-escalation of medical therapy in patients with CD who are in deep remission. This summary, along with results of key clinical studies, reviews and meta-analyses, was distributed to all panel members for review before the first round of ratings.

2.3 | Clinical scenarios and definitions

Panellists rated the appropriateness of de-escalating anti-TNF (infliximab, adalimumab, or certolizumab pegol) or IM (thiopurine or methotrexate) in the context of different clinical scenarios among patients with CD in deep remission. For all scenarios, deep remission was defined as clinical remission plus normalisation of inflammatory biomarkers (mucosal healing or normal faecal calprotectin or normal C-reactive protein) for a minimum of 6 months while on IM or anti-TNF monotherapy or combination therapy. Panel members were instructed to assume that patients were already in deep remission before de-escalation was considered, and that, if one drug of combination anti-TNF/IM therapy was stopped, the other would be continued and optimised with therapeutic drug monitoring (TDM).[21,22]

Three panel members (MPS, GYM, CAS) developed 240 scenarios within five 'chapters', each representing a distinct treatment setting. Within each chapter, panellists considered a particular de-escalation strategy in 12 patient populations: young, older and elderly males and females with complicated and uncomplicated CD. Complicated CD was defined as extensive involvement (>15 cm), history of prior resections(s), fibrostenotic, penetrating, and/or perianal disease (active or previous fissure, fistula or anal stricture); uncomplicated CD was defined as the absence of complicated disease. Young patients were defined as age 16-24 years, older as 25-64 years and elderly as ≥65 years. As appropriate, panellists were asked to distinguish between IM classes (thiopurine vs methotrexate) but not between anti-TNF agents.

Chapter 1, *On combination therapy and stopping anti-TNF*, comprised 96 scenarios. Panellists considered the appropriateness of stopping anti-TNF therapy in patients treated with IM in combination with the first or the second or subsequent anti-TNF agent. These four scenarios were considered in patients with or without prior IM failure, defined as failure or intolerance to IM monotherapy (weight-based or metabolite-based for thiopurines), necessitating escalation to anti-TNF therapy.

TABLE 1 Appropriateness of de-escalating medical therapy in patients with CD. Green indicates appropriate, yellow indicates uncertain and red indicates inappropriate. Shading indicates disagreement

Chapter			Uncomplicated CD			
On combination therapy, stopping anti-TNF	Patients with prior IM failure	On thiopurine first anti-TNF	Young male	Young female	Older male	Older female
		On thiopurine ≥ 2 anti-TNF	Young male	Young female	Older male	Older female
		On MTX first anti-TNF	Young male	Young female	Older male	Older female
		On MTX ≥ 2 anti-TNF	Young male	Young female	Older male	Older female
	Patients without prior IM failure	On thiopurine first anti-TNF	Young male	Young female	Older male	Older female
		On thiopurine ≥ 2 anti-TNF	Young male	Young female	Older male	Older female
		On MTX first anti-TNF	Young male	Young female	Older male	Older female
		On MTX ≥ 2 anti-TNF	Young male	Young female	Older male	Older female
On combination therapy, stopping IM		On thiopurine first anti-TNF	Young male	Young female	Older male	Older female
		On thiopurine ≥ 2 anti-TNF	Young male	Young female	Older male	Older female
		On MTX first anti-TNF	Young male	Young female	Older male	Older female
		On MTX ≥ 2 anti-TNF	Young male	Young female	Older male	Older female
On combination therapy, dose-reducing IM		On thiopurine first anti-TNF	Young male	Young female	Older male	Older female
		On thiopurine ≥ 2 anti-TNF	Young male	Young female	Older male	Older female
		On MTX first anti-TNF	Young male	Young female	Older male	Older female
		On MTX ≥ 2 anti-TNF	Young male	Young female	Older male	Older female
Stopping anti-TNF monotherapy		First anti-TNF	Young male	Young female	Older male	Older female
		≥2 anti-TNF	Young male	Young female	Older male	Older female
Stopping IM monotherapy		On thiopurine	Young male	Young female	Older male	Older female
		On MTX	Young male	Young female	Older male	Older female

Note: Definitions: complicated, extensive involvement (>15 cm), history of prior resections(s), fibrostenotic, penetrating and/or perianal disease (active or previous fissure, fistula or anal stricture); uncomplicated, absence of complicated disease; thiopurine, azathioprine or mercaptopurine; young, 16-24 y; older, 25-64 y; elderly, ≥65 y.
Abbreviations: CD, Crohn's disease; IM, immunomodulator therapy (thiopurine or methotrexate); anti-TNF, anti-TNF therapy (adalimumab, certolizumab pegol, or infliximab).

Chapter 2, *On combination therapy and stopping IM*, comprised 48 scenarios. Panellists considered the appropriateness of stopping IM therapy in patients treated with thiopurines or methotrexate in combination with the first or the second or subsequent anti-TNF agent.

Chapter 3, *On combination therapy and dose-reducing IM*, also comprised 48 scenarios. Panellists considered the appropriateness of reducing IM to half the usual dose, defined as a minimum of 50 mg daily of azathioprine, 25 mg daily of mercaptopurine, or 12.5 mg weekly of methotrexate, in the same four settings.

Chapter 4, *Stopping anti-TNF monotherapy*, comprised 24 scenarios, with panellists considering the appropriateness of stopping anti-TNF monotherapy in patients treated with the first or the second or subsequent anti-TNF agent.

Chapter 5, *Stopping IM monotherapy*, similarly comprised 24 scenarios, with panellists considering the appropriateness of stopping IM therapy in patients treated with thiopurines or methotrexate.

2.4 | Appropriateness panel

The panel consisted of 12 members of the Building Research in Inflammatory Bowel Disease Globally (BRIDGe) group, plus two invited panellists (EVL, DTR) with expertise in the management of inflammatory bowel disease (IBD). One additional gastroenterologist with expertise in RAND methodology (BS) moderated the panel. BRIDGe is an international collaboration among a diverse group of gastroenterologists with expertise in IBD research and care who are based in university and private practice settings, with representation from the United States, Canada, Australia and the United Kingdom (www.BRIDGeIBD.com). Our group has previously used the RAND Appropriateness Method to determine the appropriateness of concomitant IM with anti-TNF therapy for Crohn's disease,[23,24] timing and interpretation of TDM in patients with IBD using anti-TNF therapy,[25] comparative effectiveness priorities in IBD,[26] and quality in IBD endoscopy reporting.[27]

After receiving the literature summary in December 2016, panel members rated the clinical scenarios using a web-based survey platform and data were collected within two weeks. At an in-person meeting held in January 2017, the scenarios and ratings were discussed in detail, with particular focus on areas of disagreement. Agreement was not required but was discussed to ensure it was not due to misunderstanding. Panellists then re-rated each scenario and final results were tabulated and analysed.

Complicated CD							
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female
Elderly male	Elderly female	Young male	Young female	Older male	Older female	Elderly male	Elderly female

2.5 | Analysis

For each clinical scenario, median scores were calculated and rounded up, such that a median score ≥ 6.5 was considered appropriate, <6.5 and ≥3.5 was uncertain and <3.5 was inappropriate. Disagreement was assessed using the validated RAND/UCLA disagreement index.[20] A disagreement index ≥1.0 indicates extreme variation; a disagreement index value <1.0 reflects agreement. Scenarios in which ratings met criteria for disagreement were rated 'uncertain' even if the median score rating was 'inappropriate' or 'appropriate'.

3 | RESULTS

3.1 | Overall results

Of the 240 clinical scenarios evaluated, panellists rated 32 as appropriate, 149 as uncertain and 59 as inappropriate. Although agreement is not required, we found agreement in 239 of 240 scenarios. Key findings are summarised here; a detailed listing showing appropriateness ratings of the 240 scenarios in the five chapters is shown in Table 1.

3.2 | Chapter 1: On combination therapy and stopping anti-TNF

The appropriateness of stopping anti-TNF therapy in patients on combination therapy was considered in two groups of patients: those with prior IM failure and those without prior IM failure. Overall, of 96 scenarios, stopping anti-TNF therapy in patients on combination anti-TNF/IM therapy was rated as appropriate in six scenarios, uncertain in 55 scenarios and inappropriate in 35 scenarios.

In the 48 scenarios of patients with prior IM failure, 24 were rated as inappropriate, 22 as uncertain and two as appropriate. In the 48 scenarios of those without prior IM failure, 11 were rated as inappropriate, 33 as uncertain and four as appropriate. In both combination therapy groups, stopping the anti-TNF was more frequently rated inappropriate among those with complicated CD.

In patients with uncomplicated CD, among those with prior IM failure, stopping anti-TNF therapy was considered appropriate only in male and female elderly patients treated with thiopurines in combination with the first anti-TNF agent. Among those without prior IM failure, stopping anti-TNF therapy was considered appropriate in the same scenarios, as well as in those treated with methotrexate and the first anti-TNF agent. Stopping anti-TNF therapy was considered

inappropriate in young and older patients of both genders with prior IM failure treated with thiopurines or methotrexate in combination with the second or subsequent anti-TNF agent, and uncertain in all others. In those without prior IM failure, de-escalation was considered inappropriate in young males treated with thiopurines and their second or subsequent anti-TNF agent, as well as in young males and females treated with methotrexate and their second or subsequent anti-TNF agent; de-escalation was rated uncertain in all other scenarios.

In patients with complicated CD, stopping anti-TNF therapy was not considered appropriate in any patient. In patients with prior IM failure, stopping anti-TNF was considered inappropriate in young and older patients of both genders in all scenarios; the strategy was considered uncertain in male and female elderly patients. In those with complicated CD without prior IM failure, stopping anti-TNF therapy was considered inappropriate in young and older patients of both genders treated with thiopurines or methotrexate in combination with the second or subsequent anti-TNF agent. In all other scenarios, it was rated uncertain.

3.3 | Chapter 2: On combination therapy and stopping IM

In the 48 scenarios considered, stopping the IM of combination therapy was rated as appropriate in 11 scenarios, as uncertain in 35 and as inappropriate in two. In patients with uncomplicated CD on combination therapy, stopping IM was considered appropriate in all populations treated with thiopurines or methotrexate in combination with the first anti-TNF except in young females on thiopurines and young females and older males on methotrexate. In contrast, in patients with complicated CD, the strategy was considered appropriate only in elderly males and females treated with thiopurines and the first anti-TNF agent. It was considered inappropriate in young and older males on methotrexate and the second or subsequent anti-TNF agent, and uncertain in all other scenarios.

3.4 | Chapter 3: On combination therapy and dose-reducing IM

Dose-reducing IM in patients on combination therapy was considered in 48 scenarios: 15 were rated as appropriate and 33 as uncertain. No scenarios were rated inappropriate. Among those with uncomplicated CD, this strategy was considered appropriate in all populations treated with thiopurines or methotrexate and the first anti-TNF agent; it was also considered appropriate in elderly males treated with thiopurines and the second or subsequent anti-TNF agent. However, among those with complicated CD, the strategy was considered appropriate only in elderly males and females treated with thiopurines and the first anti-TNF agent. De-escalation by dose-reducing IM was rated uncertain for all other scenarios of patients with uncomplicated and complicated CD on combination therapy.

3.5 | Chapter 4: Stopping anti-TNF monotherapy

Among patients being treated with anti-TNF monotherapy, stopping treatment was not considered appropriate in any of the 24 scenarios; 14 were rated as inappropriate and 10 as uncertain. In those with uncomplicated CD, stopping anti-TNF monotherapy was considered inappropriate in young and older males and females treated with the second or subsequent anti-TNF agent, whereas all other scenarios were rated as uncertain. In those with complicated CD, stopping anti-TNF monotherapy was considered inappropriate in all scenarios except in elderly males and females treated with the first anti-TNF agent; in these two scenarios, the strategy was rated uncertain.

3.6 | Chapter 5: Stopping IM monotherapy

Similar to the strategy of stopping anti-TNF monotherapy, stopping IM monotherapy was not rated appropriate in any of the 24 scenarios considered; eight were rated as inappropriate and 16 as uncertain. In those with uncomplicated CD, it was rated uncertain in all scenarios. In those with complicated CD, the strategy was considered inappropriate in all scenarios except in elderly males and females treated with thiopurines or methotrexate, in whom it was rated uncertain. The appropriateness of stopping IM monotherapy in young males with uncomplicated CD treated with thiopurines was the only scenario in which the disagreement index showed extreme variation: four panellists rated it appropriate, three rated it inappropriate and five rated it uncertain.

4 | DISCUSSION

We considered the appropriateness of de-escalating anti-TNF or IM therapy in patients with CD in deep remission for at least 6 months. By considering this issue across a wide range of clinical scenarios, we offer guidance to practicing clinicians on how to apply available data to real-world settings.

In patients with complicated CD (extensive involvement (>15 cm), history of prior resections(s), fibrostenotic, penetrating, and/or perianal disease), we found that stopping any drug is appropriate in only a limited number of scenarios. Out of 120 scenarios in patients with complicated CD, de-escalation was rated appropriate in only four scenarios, all in elderly patients stopping or dose-reducing IM. This is consistent with data showing that complicated disease is a predictor for future relapse,[1] and with algorithms that recommend continued treatment in such patients.[17] It is notable, however, that the majority of scenarios were rated uncertain, suggesting that there may still be the opportunity to consider de-escalation after carefully assessing the risk/benefit profile of each individual patient with complicated CD.

In patients with uncomplicated CD, de-escalation was rated appropriate in 28 out of 120 scenarios. In these patients, stopping the anti-TNF or IM in patients on combination therapy was most often considered appropriate in elderly patients. Compared with those diagnosed at younger ages, elderly patients with CD typically have milder disease[28] and may be at increased risk for serious infections from combination anti-TNF/IM therapy.[29] This makes them appealing candidates for considering de-escalation. However, there remains a need to individualise each patient's risk/benefit profile,

as the benefits of de-escalation remain uncertain among those who are unable to achieve deep remission until they are treated with a second or subsequent anti-TNF therapy. In patients on combination therapy, stopping anti-TNF therapy was considered appropriate in only a minority of scenarios. Consistent with this, longer term follow-up of the STORI cohort of patients discontinuing infliximab (but continuing IM) demonstrated that only 21% of patients remain off anti-TNF treatment and free of disease complications 7 years after stopping infliximab.[30]

Importantly, panellists agreed that there is no scenario in which stopping monotherapy is considered appropriate. Studies of patients withdrawing from anti-TNF monotherapy demonstrate that up to two-thirds of patients relapse after only 12 months.[2,8,9] Among those withdrawing from azathioprine, relapse risk remains high regardless of the duration of prior treatment and increases over time,[10-13] but outcomes may vary based on extent of disease, gender and age.[31] Accordingly, we found that, among those with complicated CD, withdrawal of monotherapy is inappropriate in nearly all scenarios, but appropriateness is uncertain in most patients with uncomplicated CD, again illustrating the need for a personalised risk/benefit assessment in each patient.

Besides the risk of disease relapse, the risk of adverse events, particularly infections and malignancies, are considered when weighing the benefits of continued treatment versus de-escalation in patients with CD. Some, but not all, studies suggest an increased risk of serious and opportunistic infections in patients on anti-TNF or IM monotherapy or combination therapy for the treatment of IBD; in some studies, differences were seen between CD and ulcerative colitis (UC). A slightly increased rate of opportunistic, but not serious, infections has been seen in patients treated with IM monotherapy. A retrospective referral centre study of 100 consecutive patients with opportunistic infections showed an increased infection rate with thiopurines (OR, 3.8; 95% CI, 2.0-7.0; $P < 0.001$) but not methotrexate (OR, 4.0; 95% CI, 0.4-45.0; $P = 0.26$).[32] In SONIC, the rate of serious infections was similar among patients on azathioprine monotherapy (5.6%) compared with those on infliximab monotherapy (4.9%, $P = 0.81$) or combination therapy (3.9%; $P = 0.61$).[33] The TREAT and ENCORE registries in CD show an increased risk of serious infections in patients on infliximab monotherapy, although the magnitude of risk was small.[34,35] In contrast, a meta-analysis of 14 randomised controlled trials in IBD, including 11 trials of anti-TNF therapy and three of anti-integrin therapy, did not show an increased infection risk in CD, even though a significant 20% increase was seen among patients with UC.[36] Of note, a network meta-analysis evaluating infection risk across 49 trials in IBD involving all classes of biologic therapy showed no increased risk of serious infections with anti-TNF therapy, but an increased risk of opportunistic infections.[37]

Among studies of combination therapy, neither randomised controlled trials nor network meta-analyses have demonstrated an increased risk of serious infections in patients receiving combination therapy versus anti-TNF monotherapy.[33,38] These results should be interpreted with caution given the relatively small numbers and short duration of follow-up of patients in clinical trials. Nevertheless, higher rates of opportunistic, but not serious, infections have been reported in retrospective case-control and cohort studies of patients treated with combination therapy.[32,39] More recently, a population-based study of nearly 200,000 IBD patients demonstrated an increased risk of serious infections with anti-TNF monotherapy compared to thiopurine monotherapy, as well as an increased risk of serious and opportunistic infections with combination therapy compared to anti-TNF monotherapy.[40] Thus, the small increased risk of serious and opportunistic infections with combination therapy, or IM or anti-TNF monotherapy must be balanced against the well-recognised increased risk of serious infections associated with underlying disease activity or corticosteroid use.[34,41]

Another rationale for de-escalation of medical therapy is to reduce the risk of malignancy, particularly the risk for nonmelanoma skin cancer (NMSC) and non-Hodgkin's lymphoma (NHL) associated with thiopurine use. Population-based cohort studies as well as case-control studies show a three- to six-fold increase in NMSC risk with thiopurine use.[42,43] Although these cancers are rarely life-threatening, the increased risk may warrant regular dermatological screening for patients receiving thiopurines in regions with high ultraviolet radiation exposure.

Most concerning for clinicians is the association between thiopurine use and NHL risk, which has been estimated from meta-analyses and large population-based cohorts as four- to six-fold higher than the general population. Males are at increased risk and, although the relative risk is highest in young patients, the absolute risk is highest in older patients.[44-46] Of note, younger males under age 35 have a particular risk for the aggressive hepatosplenic T-cell lymphoma (HSTCL), which has most commonly been associated with prior thiopurine exposure.[47] Although the risk is small, it causes great concern to clinicians given the extremely poor prognosis of HSTCL, and is an incentive to stop thiopurine therapy in young males. This very small risk must be weighed against the benefits of achieving tight disease control in each individual young patient. Indeed, disagreement among the panellists occurred in only one scenario: appropriateness of stopping thiopurine monotherapy in young males with uncomplicated CD. This may reflect the complexity and uncertainty around decision-making in this patient subgroup.

Whether anti-TNF monotherapy increases the risk of NHL is less clear. A meta-analysis of 26 studies of anti-TNF therapy found a significantly increased NHL risk, with the highest risk among males age 20-54. However, nearly all patients who developed NHL had current or prior thiopurine exposure and, when compared with the NHL rate in CD patients treated with IM therapy alone, there was no significant difference.[44] Similarly, although a recent large French cohort study using insurance data from nearly 200 000 patients demonstrated an increased risk of lymphoma in IBD patients treated with anti-TNF monotherapy, 35% of anti-TNF patients were previously exposed to a thiopurine for a mean of 12 months. Details of the analysis in nonthiopurine-exposed patients are not shown, although the authors state that the association between anti-TNF monotherapy and lymphoma risk is retained.[48] Additional studies in patients treated with anti-TNF therapy without prior thiopurine exposure are

needed to help clarify whether anti-TNF therapy alone is associated with an increased risk of lymphoma.

The appropriateness of de-escalation of medical therapy in CD patients was rated uncertain in more than 60% of scenarios in our study. Hopefully some of this uncertainty will be addressed by ongoing studies such as SPARE and STOP IT,[18,19] which are prospectively evaluating the benefits of discontinuing infliximab or IM in patients with CD who achieve deep remission on combination therapy. SPARE will prospectively evaluate relapse and remission rates using objective clinical endpoints after pre-specified de-escalation strategies.[18] The STOP-IT study will increase our understanding of the role of anti-TNF TDM as a variable in the de-escalation decision-making process, given that drug concentrations and antibody levels are known to affect treatment outcomes after de-escalation.[9,25,49]

Nevertheless, translating study data to practice will prove challenging, given that the complexity of variables present during clinical decision-making exceeds those that are readily measurable in clinical trials. For example, most endpoints of prior and ongoing studies measure disease activity in a time-dependent manner. This does not incorporate the more global, longitudinal measurement of disease severity that is less easily quantified but impacts equally, or more, on an individual patient's quality of life. De-escalation of therapy is likely to be less appropriate in a patient presenting with low disease activity but with high overall disease severity. Acknowledgement of the importance and quantification of disease severity has recently emerged as an important research priority that should be incorporated into the design of future de-escalation studies.[50,51]

This study has some limitations that may affect applicability of our findings to current clinical practice. First, we did not distinguish between anti-TNF therapies. Infliximab, adalimumab and certolizumab pegol are all effective at inducing and maintaining remission in CD, whether given as monotherapy or in combination with IM.[52] Although prospective head-to-head comparative effectiveness studies have not been performed, some, but not all, retrospective studies suggest that combination therapy with infliximab is less immunogenic and therefore potentially more efficacious than combination therapy with other anti-TNFs, including adalimumab.[53-55] Our findings may have been different if panellists were presented with scenarios involving individual anti-TNF agents rather than the class of drug.

Second, we did not include TDM as an independent variable for consideration in the de-escalation decision-making process. Also, in considering appropriateness of de-escalating therapy in a patient on combination anti-TNF/IM therapy, we assumed that if one drug were stopped, the other would be continued and proactively optimised with TDM. We acknowledge that proactive optimisation of either IM or anti-TNF therapy is not yet widely supported by clinical guidelines, and further research is required to confirm optimal drug levels, in particular of anti-TNF agents, in individual patient scenarios.[56,57]

Third, per RAND methodology, we did not consider regulatory issues such as drug availability, prescribing restrictions and cost of therapy. We recognise that these are important, practical considerations in real-world treatment decisions, including de-escalation, especially in scenarios where clinical evidence is equivocal.

Finally, although panellists considered 240 patient scenarios, we acknowledge that this may represent only a small portion of possible clinical scenarios encountered in practice. We also did not weight levels of appropriateness to help clinicians select among multiple potentially viable de-escalation strategies; we acknowledge that this is an over-simplification of the individualised decision-making processes utilised by clinicians in real-world practice.

5 | CONCLUSIONS

Using an evidence-based approach to guide expert opinion, we found that de-escalating medical therapy in CD patients in deep remission is only appropriate in a minority of carefully selected patients. This includes patients with uncomplicated disease and the elderly, in whom the benefits of de-escalation may outweigh the risks of continuing medical therapy, in particular with thiopurines. De-escalation was considered inappropriate in one-fourth of scenarios, primarily in patients with complicated disease and in patients on monotherapy. In patients on combination therapy, de-escalation was more likely to be considered inappropriate if patients had previously failed at least one anti-TNF and/or IM. In nearly two-thirds of scenarios, across all chapters, there was uncertainty regarding the appropriateness of de-escalation.

Ongoing trials (SPARE, STOP-IT)[18,19] prospectively evaluating outcomes among patients who discontinue anti-TNF or IM therapy are likely to help address these significant outstanding knowledge gaps. In the meantime, our results provide a framework for clinicians contemplating when de-escalation may be appropriate, and underscore the importance of individualising risk/benefit profiles in all treatment decisions. We hope that these results will help clinicians make rational decisions in the face of significant uncertainty when considering de-escalation of medical therapies in Crohn's disease.

ACKNOWLEDGEMENTS

Editorial support in the form of medical writing and assembling tables was provided by Shira Berman and paid for by the BRIDGe Group.

Declaration of personal interests: This work was supported by unrestricted educational grants from Takeda, Pfizer and Abbvie. MPS has received educational grants or research support from Ferring and Orphan; has received speakers' fees from Janssen, Abbvie, Ferring, Takeda, Pfizer, Celgene, MSD and Shire; and has served on advisory boards for Janssen, Takeda, Pfizer, Celgene, Abbvie, MSD. GYM has served as a consultant for Abbvie, Janssen, UCB, Takeda, Genentech, Luitpold, Celgene, Pfizer, Samsung Bioepis and Given Imaging, and has received research support from Prometheus Labs. SMD has served as a speaker for Abbvie, Janssen and Takeda and participated in advisory boards for Abbvie, Janssen, Ferring, Takeda and Shire. LER has served as a consultant to Ferring. All

honoraria are paid to Mayo Clinic. EVL has consulted for AbbVie, Allergan, Amgen, Celgene, Celltrion Healthcare, Eli Lilly, Janssen, Napo Pharmaceuticals, Pfizer, Takeda and UCB Pharma; and has received research support from AbbVie, Amgen, Celgene, Genentech, Gilead, Janssen, Medimmune, Pfizer, Robarts Clinical Trials, Seres Therapeutics, Takeda and UCB Pharma. DTR has consulted for Abbvie, Abgenomics, Allergan Inc., Ferring Pharmaceuticals Inc., Genentech/Roche, Janssen Pharmaceuticals, Merck & Co. Inc., Medtronic, Pfizer, Takeda, Target PharmaSolutions, Inc; and has received research support from Abbvie, Genentech/Roche, Janssen Pharmaceuticals, Takeda. LB has served as a consultant for Pfizer, Janssen, Shire and Takeda, and served as speaker for Janssen, Shire and Takeda. BB has served as an advisor/speaker for Shire, Ferring, Janssen, Abbvie, Takeda, Actavis, Pfizer. Has served as an advisor for Robarts Clinical Trials, Celgene, Microbiome Insights, Merck, Amgen, Pendopharm, Genentech, Celltrion, Allergan, Protagonist. Has received research support from Janssen, Abbvie, GSK, BMS, Amgen, Genentech, Merck, RedHill Biopharm, BI, Qu Biologic, Celgene, Alvine. Has stock options in Qu Biologic. ASC has served as a consultant to Abbvie, Janssen, UCB, Takeda, Pfizer, Miraca Laboratories, Samsung, Alfasigma and Arena. PMI has received advisory fees from Abbvie, Warner Chilcott, Takeda, MSD, Vifor Pharma, Pharmacosmos, Topivert, Genentech, Hospira, Samsung Bioepis; lecture fees from Abbvie, Warner Chilcott, Ferring, Falk Pharma, Takeda, MSD, Johnson and Johnson, Shire; financial support for research: MSD, Takeda. JJ has served as a speaker for Jansen, Merck, Schering-Plough, Abbot and Abbvie; and has participated in advisory boards for Janssen, Abbott and Takeda. GGK has served as a speaker for Janssen, Abbvie and Pfizer; has received research support from Merck, Abbvie and Shire. CAS has served as a consultant/advisory board for Abbvie, Amgen, Celgene, Lilly, Janssen, Sandoz, Pfizer, Prometheus, Sebela, Takeda; speaker for CME activities: Abbvie, Janssen, Pfizer, Takeda; has received grant support: Abbvie, Janssen, Pfizer, Takeda. For the remaining authors none were declared.

AUTHORSHIP

Guarantor of the article: Miles P. Sparrow.

Author contributions: MPS, study design, panellist, data collection, data interpretation, writing and critical review of manuscript; CAS, study design, panellist, data collection, data interpretation, critical review of manuscript; GYM, study design, panellist, data collection, data interpretation, critical review of manuscript; SD, LR, EVL Jr, DTR, LB, AC, PI, JJ and GGK, panellist, critical review of manuscript; PK, BB and FV: critical review of manuscript; BS, panel moderator, critical review of manuscript. All authors approved the final version of the manuscript.

ORCID

Miles P. Sparrow https://orcid.org/0000-0003-2527-8044
Edward V. Loftus Jr https://orcid.org/0000-0001-7199-6851
David T. Rubin https://orcid.org/0000-0001-5647-1723
Gilaad G. Kaplan https://orcid.org/0000-0003-2719-0556

REFERENCES

1. Torres J, Boyapati RK, Kennedy NA, Louis E, Colombel JF, Satsangi J. Systematic review of effects of withdrawal of immunomodulators or biologic agents from patients with inflammatory bowel disease. *Gastroenterology*. 2015;149:1716-1730.
2. Kennedy NA, Warner B, Johnston EL, et al. Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease: an observational study, plus systematic review and meta-analysis. *Aliment Pharmacol Ther*. 2016;43:910-923.
3. Gisbert JP, Marin AC, Chaparro M. The risk of relapse after anti-TNF discontinuation in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2016;111:632-647.
4. Van Assche G, Magdelaine–Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology*. 2008;134:1861-1868.
5. Kierkuś J, Iwańczak B, Wegner A, et al. Monotherapy with infliximab versus combination therapy in the maintenance of clinical remission in children with moderate to severe Crohn disease. *J Pediatr Gastroenterol Nutr*. 2015;60:580-585.
6. Del Tedesco E, Paul S, Marotte H, et al. Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: a prospective study. *Gastroenterology*. 2016;150:S143-S144.
7. Van Steenbergen S, Bian S, Vermeire S, Van Assche G, Gils A, Ferrante M. Dose de-escalation to adalimumab 40 mg every 3 weeks in patients with Crohn's disease - a nested case-control study. *Aliment Pharmacol Ther*. 2017;45:923-932.
8. Bortlik M, Duricova D, Machkova N, et al. Discontinuation of anti-tumor necrosis factor therapy in inflammatory bowel disease patients: a prospective observation. *Scand J Gastroenterol*. 2016;51:196-202.
9. Ben-Horin S, Chowers Y, Ungar B, et al. Undetectable anti-TNF drug levels in patients with long-term remission predict successful drug withdrawal. *Aliment Pharmacol Ther*. 2015;42:356-364.
10. Lémann M, Mary J-Y, Colombel J-F, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology*. 2005;128:1812-1818.
11. Treton X, Bouhnik Y, Mary J, et al. Azathioprine withdrawal in patients with Crohn's disease maintained on prolonged remission: a high risk of relapse. *Clin Gastroenterol Hepatol*. 2009;7:80-85.
12. Wenzl HH, Primas C, Novacek G, et al. Withdrawal of long-term maintenance treatment with azathioprine tends to increase relapse risk in patients with Crohn's disease. *Dig Dis Sci*. 2015;60:1414-1423.
13. Vilien M, Dahlerup JF, Munck LK, Norregaard P, Gronbaek K, Fallingborg J. Randomized controlled azathioprine withdrawal after more than two years treatment in Crohn's disease: increased relapse rate the following year. *Aliment Pharmacol Ther*. 2004;19:1147-1152.
14. Fischer M, Campbell SC, Johnson CS, et al. Risk factors for rescue therapy in Crohn's patients on combination therapy after discontinuation of the immunomodulator. *Gastroenterology*. 2014;146:S450.
15. Gisbert JP, Marin AC, Chaparro M. Systematic review: factors associated with relapse of inflammatory bowel disease after discontinuation of anti-TNF therapy. *Aliment Pharmacol Ther*. 2015;42:391-405.
16. Oussalah A, Chevaux JB, Fay R, Sandborn WJ, Bigard MA, Peyrin-Biroulet L. Predictors of infliximab failure after azathioprine withdrawal in Crohn's disease treated with combination therapy. *Am J Gastroenterol*. 2010;105:1142-1149.

17. Pariente B, Laharie D. Review article: why, when and how to de-escalate therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2014;40:338-353.
18. ClinicalTrials.gov. A proSpective Randomized Controlled Trial comParing infliximAb-antimetabolites Combination Therapy to Anti-metabolites monotheRapy and Infliximab monothErapy in Crohn's Disease Patients in Sustained Steroid-free Remission on Combination Therapy (SPARE). https://ClinicalTrials.gov/ct2/show/NCT02177071. Accessed June 25, 2017.
19. Buhl SS, Steenholdt C, Brynskov J, Thomsen OO, Bendtzen K, Ainsworth MA. Discontinuation of infliximab therapy in patients with Crohn's disease in sustained complete remission (the STOP IT study): protocol for a double-blind, randomised, placebo-controlled, multicentre trial. *BMJ Open*. 2014;4:e005887.
20. Brook RH. *The RAND/UCLA appropriateness method. Clinical practice guideline development: methodology perspectives*. Rockville, MD: Public Health Service, AHCR; 1994.
21. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology*. 2015;148:1320-1329.e3.
22. Gilissen L, Wong DR, Engels LG, et al. Therapeutic drug monitoring of thiopurine metabolites in adult thiopurine tolerant IBD patients on maintenance therapy. *J Crohns Colitis*. 2012;6:698-707.
23. Melmed GY, Spiegel BM, Bressler B, et al. The appropriateness of concomitant immunomodulators with anti-tumor necrosis factor agents for Crohn's disease: one size does not fit all. *Clin Gastroenterol Hepatol*. 2010;8:655-659.
24. Melmed GY, Kaplan GG, Sparrow MP, et al. Appropriateness of combination therapy for patients with inflammatory bowel diseases: one size still does not fit all. *Clin Gastroenterol Hepatol*. 2018;16:1829-1831.
25. Melmed GY, Irving PM, Jones J, et al. Appropriateness of testing for anti-tumor necrosis factor agent and antibody concentrations, and interpretation of results. *Clin Gastroenterol Hepatol*. 2016;14:1302-1309.
26. Cheifetz AS, Melmed GY, Spiegel B, et al. Setting priorities for comparative effectiveness research in inflammatory bowel disease: results of an international provider survey, expert RAND panel, and patient focus groups. *Inflamm Bowel Dis*. 2012;18:2294-2300.
27. Devlin SM, Melmed GY, Irving PM, et al. Recommendations for quality colonoscopy reporting for patients with inflammatory bowel disease: results from a RAND appropriateness panel. *Inflamm Bowel Dis*. 2016;22:1418-1424.
28. Fumery M, Pariente B, Sarter H, et al. Natural history of Crohn's disease in elderly patients diagnosed over the age of 70 years: a population-based study. *Inflamm Bowel Dis*. 2016;22:1698-1707.
29. Saad AM, Czul F, Sakuraba A, Rubin DT, Cohen RD. Age of diagnosis is associated with disease presentation and therapeutic complications in patients with Crohn's disease. *Inflamm Bowel Dis*. 2016;22:1027-1031.
30. Reenaers C, Mary J-Y, Nachury M, et al. Outcomes 7 years after infliximab withdrawal for patients with Crohn's disease in sustained remission. *Clin Gastroenterol Hepatol*. 2018;16:234-243.e2.
31. Kirchgesner J, Beaugerie L, Carrat F, Sokol H, Cosnes J, Schwarzinger M. Impact on life expectancy of withdrawing thiopurines in patients with Crohn's disease in sustained clinical remission: a lifetime risk-benefit analysis. *PLoS ONE*. 2016;11:e0157191.
32. Toruner M, Loftus EV, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology*. 2008;134:929-936.
33. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362:1383-1395.
34. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. *Am J Gastroenterol*. 2012;107:1409-1422.
35. D'Haens G, Reinisch W, Colombel JF, et al. Five-year safety data from ENCORE, a European observational safety registry for adults with Crohn's disease treated with infliximab [Remicade(R)] or conventional therapy. *J Crohns Colitis*. 2017;11:680-689.
36. Shah ED, Farida JP, Siegel CA, Chong K, Melmed GY. Risk for overall infection with anti-TNF and anti-integrin agents used in IBD: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2017;23:570-577.
37. Bonovas S, Fiorino G, Allocca M, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14:1385-1397.e10.
38. Wheat CL, Ko CW, Clark-Snustad K, Grembowski D, Thornton TA, Devine B. Inflammatory bowel disease (IBD) pharmacotherapy and the risk of serious infection: a systematic review and network meta-analysis. *BMC Gastroenterol*. 2017;17:52.
39. Osterman MT, Haynes K, Delzell E, et al. Effectiveness and safety of immunomodulators with anti-tumor necrosis factor therapy in Crohn's disease. *Clin Gastroenterol Hepatol*. 2015;13:1293-1301 e1295; quiz e1270, e1272.
40. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology*. 2018;155:337-346.
41. Osterman MT, Sandborn WJ, Colombel J-F, et al. Crohn's disease activity and concomitant immunosuppressants affect the risk of serious and opportunistic infections in patients treated with adalimumab. *Am J Gastroenterol*. 2016;111:1806-1815.
42. Peyrin–Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology*. 2011;141:1621-1628.e5.
43. Long MD, Herfarth HH, Pipkin CA, Porter CQ, Sandler RS, Kappelman MD. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2010;8:268-274.
44. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol*. 2009;7:874-881.
45. Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. *Clin Gastroenterol Hepatol*. 2015;13:847-858 e844; quiz e848–850.
46. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet*. 2009;374:1617-1625.
47. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2011;9:36-41.e1
48. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. *JAMA*. 2017;318:1679-1686.
49. Louis E, Mary JY, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology*. 2012;142:63-70 e65; quiz e31.
50. Siegel CA, Whitman CB, Spiegel B, et al. Development of an index to define overall disease severity in IBD. *Gut*. 2018;67:244-254.

51. Peyrin-Biroulet L, Panés J, Sandborn WJ, et al. Defining disease severity in inflammatory bowel diseases: current and future directions. *Clin Gastroenterol Hepatol*. 2016;14:348-354.e17.
52. Jones JL, Kaplan GG, Peyrin-Biroulet L, et al. Effects of concomitant immunomodulator therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease: a meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol*. 2015;13:2233-2240 e2231–2232; quiz e2177–2238.
53. Doecke JD, Hartnell F, Bampton P, et al. Infliximab vs. adalimumab in Crohn's disease: results from 327 patients in an Australian and New Zealand observational cohort study. *Aliment Pharmacol Ther*. 2017;45:542-552.
54. Benmassaoud A, Al-Taweel T, Sasson MS, et al. Comparative effectiveness of infliximab versus adalimumab in patients with biologic-naive Crohn's disease. *Dig Dis Sci*. 2017;63:1302-1310.
55. Varma P, Paul E, Huang C, Headon B, Sparrow MP. A retrospective comparison of infliximab versus adalimumab as induction and maintenance therapy for Crohn disease. *Intern Med J*. 2016;46:798-804.
56. Mitrev N, Vande Casteele N, Seow CH, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2017;46:1037-1053.
57. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. *Gastroenterology*. 2017;153:827-834.

How to cite this article: Sparrow MP, Melmed GY, Devlin S, et al. De-escalating medical therapy in Crohn's disease patients who are in deep remission: A RAND appropriateness panel. *GastroHep*. 2019;1:108–117. https://doi.org/10.1002/ygh2.337