Expert Forum

IBD Ahead 2010: National Meeting

Making Education Easy 4th Annual Exchange on Advances in IBD – May 2010

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About Expert Forums

Expert Forum publications are designed to encapsulate the essence of a local meeting of health professionals who have a keen interest in a condition or disease state. These meetings are typically a day in duration, and will include presentations of local research and discussion of guidelines and management strategies.

Even for local events it is not always possible for everyone with a similar therapeutic interest to attend. Expert Forum publications capture what was said and allows it to be made available to a wider audience through the Research Review membership or through physical distribution.

Welcome to this review of the recent New Zealand Meeting of IBD Ahead 2010 - 4th Annual Exchange on Advances in Inflammatory Bowel Disease, which was held in Wellington.

This meeting formed part of an international consultation process that has identified 10 key questions relating to the use of corticosteroids and immunosuppressants in inflammatory bowel disease (IBD). Draft answers, prepared in conjunction with an International Steering Committee, were the focus of discussion. An invitation extended to all members of the New Zealand Society of Gastroenterology, brought together 16 gastroenterologists with expertise and interest in the treatment of IBD.

The IBD Ahead process is an initiative intended to stimulate national and international discussion of evidence-based practice in IBD. The 4th annual cycle of this process considers the use of corticosteroids (CS) and immunosuppressants in the management of IBD. The overall objectives of the 2010 IBD Ahead programme are 3-fold. Firstly, to discuss ways to improve disease control in IBD. Secondly, to outline key clinical data and experience leading to optimisation of CS and immunosuppressive use in Crohn's disease (CD). And finally, to discuss and exchange ideas on best practice in topics of current interest in CD. An international consultation process (see Figure 1) identified 10 key questions in IBD. Draft answers have been prepared by four bibliographic fellows** in conjunction with the International Steering Committee (ISC),*** and were the focus of discussion at the New Zealand IBD Ahead meeting.

*****Bibliographic Fellows: Marc Ferrante (Belgium), Konstantinos Karmiris (Greece), Evan Newnham (Australia), Jesse Siffledeen (Canada), Zuzana Zelinkova (The Netherlands)***

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Figure 1: Overview of IBD Ahead 2010 programme.

The New Zealand IBD Ahead meeting was conducted in the following manner: For each question, the proposed draft answer and evidence from the literature was presented by a member of the National Steering Committee. The question was then discussed by the group and draft answers challenged and modified where necessary to reflect personal experience and expert opinion for best practice within New Zealand. After discussion and modification of the answer, delegates individually assigned an agreement score (1-9; strongly disagree – strongly agree) using electronic key pads. Consensus was reached if >75% of delegates voted to agree (agreement score 7-9) or

disagree (agreement score 1-3). The level of endorsement is indicated by the mean score. If no consensus was reached (either for or against) then the draft answer was further modified and the vote repeated until consensus was reached. New Zealand was the 4th country to hold a national meeting after Ireland, Norway and France. The modified answers will be submitted to the ISC for integration with those from other participating countries for the purpose of generating educational case studies.

It was the consensus that the term immunosuppressant should be used in its broad sense and refer to all medications used to suppress immune function, including CS. The terms biologic or biological refer to anti-tumour necrosis factor (TNF) antibody medications and the term immunomodulator refers to non-corticosteroid, non-biologic immunosuppressants. As none of the delegates were paediatric gastroenterologists, the discussion considered adult IBD only. The level of evidence for each answer has been determined using the University of Oxford Centre for Evidence-Based Medicine system (see Figure 2).

Evidence level	Definition
1a	Systematic review (with homogeneity) of randomized controlled trials
1b	Individual randomized controlled trial (with narrow Confidence Intervals)
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality randomized controlled trial e.g. <80% follow-up)
2c	'Outcomes' research; ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles

Figure 2: Levels of evidence supporting answers.

This educational summary reports the discussions and views of the group in the context of evidence presented at the IBD Ahead National Meeting. In this report, modifications to the draft answer are indicated as follows: Deletions, text scored through. Additions, text in bold italic script.

Question 1 **Presented by Associate Professor Richard Gearry**

When should we introduce corticosteroids and for how long?

NZ Modified Answer

Systemic corticosteroids should be introduced in severely active Crohn's disease of any location and in colonic disease of moderate-to-severe activity. ***Exceptions to this may include predominant perianal disease, abscess and impending surgery.*** (Level of evidence: 1a)

Consensus agreement 94%: Mean endorsement 8.18

Budesonide is ~~preferred~~ ***an acceptable alternative*** to systemic corticosteroids in moderately active ileocaecal disease. (1a)

Consensus agreement 86%: Mean endorsement 7.9

The duration of initial treatment with systemic corticosteroids at full dose might vary depending on the response of the patient. ~~There is no clear evidence that continuing the full dose beyond weeks 1-3 influences remission rates.~~ ***If there is no response by week 4 of full-dose-steroid therapy, alternative treatments need to be considered.*** (2b)

Consensus agreement 93%: Mean endorsement 8.1

Discussion

In the modern era of immunomodulator and biologic therapy, the pre-eminent role of CS as a first-line agent in CD can be challenged. CS have proven effect in controlling symptoms in CD, however, their ability to induce mucosal healing and thereby provide prolonged remission is limited.[1] A significant number of patients (approximately 20%) fail to respond to CS treatment (steroid resistance), and approximately one-third become steroid dependant. Adverse events related to CS use are common, with particular concern related to infectious and post-operative complications.[2] Furthermore, cohort studies have indicated that the early use of CS in CD may be associated with adverse long-term outcomes.[3] Despite these limitations, delegates agreed that CS remain an important first-line agent for the management of CD. While effective in controlling inflammatory disease, delegates felt strongly that a distinction was required between this and fistulating or penetrating disease. Indeed, in the presence of fistulating disease, CS increase the incidence of abscess formation and peritonitis, and their use should be avoided. Furthermore, delegates agreed that where surgery is inevitable or imminent, the adverse effect of CS on surgical outcome should contraindicate their use where possible.

Modified-release preparations of budesonide are designed to deposit the agent in the inflamed ileocaecum while limiting systemic exposure by means of extensive first-pass metabolism. Budesonide is effective for the treatment of moderately-active ileocaecal Crohn's disease with efficacy intermediate between that of prednisolone and mesalazine. Due to cost considerations in New Zealand, budesonide is only subsidised for use in patients who have either a cushingoid habitus, or those who suffer from diabetes, osteoporosis or develop severe acne following treatment with conventional CS therapy. Clinical experience with budesonide was therefore limited within our forum. Delegates disagreed that budesonide was preferred to systemic CS (prednisone) in moderately active ileocaecal CD, arguing that this unduly sacrificed efficacy for a better side-effect profile. Delegates suggested that in such a situation, where symptoms often settle rapidly with prednisone, a short course of prednisone would be both effective and limit systemic CS exposure. Several delegates proposed clinical scenarios where budesonide might be preferred, for example, in young female patients, however, consensus was reached with a modified answer.

Delegates' usual method of prescribing corticosteroids is to have a variable length induction course; 40 mg/day until clinical response (or for some, remission), followed by a tapering phase. Delegates felt it was counterintuitive to reduce the CS dose prior to symptomatic response, but agreed that some time limit on full-dose treatment was required. No evidence was presented that supported one approach over another. The group recommended limiting the CS induction phase (full dose) to 4 weeks in line with the published definition of steroid resistance. If after 4 weeks there has been little or no response, alternative therapies must be considered if they haven't been already. The group stressed that 4 weeks at full dose is not the optimal prescription, but an absolute maximum exposure to high-dose CS in this setting. It was the unanimous opinion of the group that overall CS exposure should be minimised.

Question 2 Presented by Associate Professor Richard Gearry

What is the best dosing strategy for the use of corticosteroids in patients with Crohn's disease, in terms of; starting and maximum dose, duration, dose escalation/de-escalation (When? Rate?), formulation, avoiding side effects? What duration of corticosteroid treatment is linked to the occurrence of side effects?

NZ Modified Answer

An acceptable initial ~~The optimal initial~~ dose of systemic corticosteroids ***(oral prednisone)*** in Crohn's disease ranges from 40-60 mg/day (adult population) ~~to 1mg/kg.~~ (2b)
Consensus agreement 87%: Mean endorsement 8.0

The optimal starting dose of budesonide is 9 mg/day. (1a)
Consensus agreement 100%: Mean endorsement 8.9

The duration of initial treatment with systemic corticosteroids at full dose might vary depending on the response of the patient. ~~There is no clear evidence that continuing the full dose beyond weeks 1-3 influences remission rates.~~ ***If there is no response by week 4 of full-dose-steroid therapy, alternative treatments need to be considered.*** (2b)
Consensus agreement 100%: Mean endorsement 8.7

~~A tapering regimen of systemic corticosteroids does not seem to influence short- or long-term remission rates.~~ ***In steroid-responsive patients, there is no evidence to support any particular steroid-tapering duration. In terms of remission rates, steroid-tapering duration should be tailored to the patient.*** (4)
Consensus agreement 80%: Mean endorsement 7.8

No data are available to allow evaluation of any benefit of escalation of steroid dose (i.e. when steroids have already been started ***at an appropriate dose*** for induction of remission).
Consensus agreement 94%: Mean endorsement 8.0

Neither systemic steroids nor budesonide have been shown to be effective in maintenance of remission. (1a)
Consensus agreement 100%: Mean endorsement 8.7

Corticosteroids have been shown to increase the risk of serious and opportunistic infections, both independently and in combination with immunosuppressive and biologic agents. Thus, the best option to prevent steroid-induced side effects is to avoid prolonged or repetitive use and to switch appropriate patients to ~~immunosuppressive therapy~~ alternative ***medical or surgical therapy.*** (2b)
Consensus agreement 100%: Mean endorsement 8.8

To ***help*** prevent steroid-induced loss of bone mineral density, ~~calcium and~~ vitamin D supplements should be provided ***and one should ensure adequate dietary intake of calcium***. Not all steroid-induced side effects occur dose- or time-dependently. (2b)
Consensus agreement 94%: Mean endorsement 8.0

Discussion

With the exception of budesonide[4], formal dose-finding studies have not been performed for CS in IBD. The use of CS in CD has, however, been investigated in numerous early studies and, remarkably, the response and remission rates found were similar irrespective of preparation or dose (30mg prednisolone – 1 mg/kg prednisolone per day).[1] In line with the unanimous opinion that systemic CS exposure should be limited, and consistent with standard medical practice in New Zealand, the group agreed that initial treatment doses should not be greater than 40-60mg oral prednisone per day. This dosage therefore constitutes full-dose CS that should not be continued beyond 4 weeks maximum duration, prior to tapering. In respect of tapering; only one study has investigated the relative merits of rapid tapering (over 4 weeks) compared with slow tapering (over 12 weeks) after the induction of remission with IM methylprednisolone (for 3 weeks). No significant difference in relapse rate was found, either at the end of each protocol (85% and 87%, respectively), or at 6 months.[5] Delegates indicated that in clinical practice, the rate at which they taper steroids was influenced by a number of factors including disease severity, speed of response to CS and a desire to minimise side effects. The group recognised the appropriate use of IV CS in the inpatient treatment of severe inflammatory CD, but did not discuss this further.

There is no evidence to support the use of steroids as maintenance therapy in CD. In steroid-dependant disease, however, clinical experience shows that low-dose CS may maintain remission. The semantic differences between these two positions was hotly debated but the group maintained their previous opinion that as a rule, long-term steroid use is not desirable and reasonable efforts should be made to achieve steroid-free remission. Furthermore, decisions must be individualised and open, and the group recommends collegiate discussion if long-term steroid use seems inevitable.

In the biological era, much has been made of the adverse safety profiles of modern immunosuppressive therapy. The widespread and common use of CS in clinical practice should not, however, avert us to the significant side-effect profile of these drugs. Analysis of data from The Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry reveals that patients treated with CS are twice as likely to suffer severe infectious or fatal events[6], and a retrospective case-control study from Liverpool associated recent steroid use with a significant increased risk of intra-abdominal or pelvic sepsis. The significant risks associated with CS are compounded when used in combination with other immunosuppressants (discussed in Question 6). Failure of CS to induce mucosal healing and maintain remission in addition to their adverse risk profile should encourage early introduction of disease-modifying agents or surgery where appropriate.

Crohn's disease is associated with osteoporosis through diverse mechanisms including exposure to CS (even at a low dose such as 7 mg/day).[7] National guidelines continue to incorporate recommendations for the use of calcium and vitamin D supplementation to mitigate steroid-induced bone loss.[8, 9] Investigation of the effectiveness of such strategies has, however, produced conflicting results. In addition to this, delegates highlighted concerns over reports of excess mortality associated with routine calcium supplementation.[10] With such uncertainty, the group felt the most appropriate current strategy was routine supplementation of Vitamin D (to a group at high risk of vitamin D insufficiency) during CS treatment, and optimisation of dietary calcium. A show of hands, however, revealed that most delegates continued to co-prescribe calcium and vitamin D supplements with CS.

Question 3 Presented by Professor Murray Barclay

How early should immunosuppressives be introduced in the management of Crohn's Disease and which regimen should be used?

NZ Modified Answer

Initiation of immunosuppressives early in the disease course (~~at diagnosis~~) should be considered in ***all*** patients ~~at high risk of complicated disease~~ ***except those with mild disease*** (1b)
Consensus agreement 94%: Mean endorsement 8.4

Immunomodulators are indicated in immunomodulator-naive patients starting ~~systemic steroids or~~ infliximab in order to achieve ~~steroid sparing effects or~~ added benefit. ***There are no randomised prospective data regarding this approach with other biologics*** (1b)
Consensus agreement 100%: Mean endorsement 8.4

Purine analogues are indicated in post-operative prophylaxis ***in most patients*** immediately after surgical resection of ileocolonic disease. (1a)
Consensus agreement 82%: Mean endorsement 7.5

Evidence for the use of purine analogues as first-line therapy in perianal fistulating Crohn's disease is limited. (2)
Consensus agreement 76%: Mean endorsement 7.6

Discussion

Crohn's disease is a lifelong relapsing condition with 20% of patients displaying active disease during each of the first 7 years following diagnosis. Forty percent of Crohn's disease patients require surgery after 10 years of disease and 80% in their lifetime.[11] Factors associated with disease progression have been defined; age <40 years, smoking status, the presence of small bowel or perianal disease.[3] However, a significant minority of those with few or no risk factors will suffer complicated disease. In view of this significant disease burden and knowledge that early introduction of immunosuppressants may slow progression, the group agreed that as a rule, all patients (except those with mild disease) should be considered for immunosuppressive therapy early in their disease course.

The immunomodulators, azathioprine (AZA) and 6-mercaptopurine (6-MP), collectively the thiopurines, and methotrexate (MTX), are all effective agents for the treatment of CD, and in particular the maintenance of remission (their onset of action is generally too slow for them to be considered effective induction agents). The rapidly effective biologicals on the other hand are effective induction and maintenance agents. The co-prescription of AZA with infliximab (IFX) in immunomodulator naive patients has been investigated in the Study of Biologic and Immunomulator Naive Patients in Crohn's Disease (SONIC) trial and previously by the Groupe d'Etude Therapeutique des Affections Inflammatoires du Tube Digestif (GETAID).[12,13] Outcomes in both studies were similar. In SONIC, 57% of patients receiving IFX and AZA achieved steroid-free remission at 26 weeks compared with 44% of those receiving IFX monotherapy, and 30% of those receiving AZA alone; 44%, 30% and 17% achieved mucosal healing in each group, respectively. Adverse events were similar between the groups. Similar randomised controlled trials have not been performed with other biologic agents.

Following resectional surgery for CD, 72% of patients have endoscopic recurrence and 20-30% have symptomatic relapse after 1 year.[14] The mesalazine drugs, metronidazole and the thiopurines have all been shown to reduce recurrence, with AZA providing better results than mesalazines in head-to-head studies. In patients requiring surgery despite established AZA therapy, continuing the medication post-operatively provides continued benefit, especially if disease was penetrating or perforating.[15] In view of this, and supported by evidence presented from Cochrane meta-analysis, the group agreed that post-operative prophylaxis with thiopurines was warranted. Delegates offered some exceptions to the rule, for example, if a significant period had elapsed between the onset of disease and the need for surgery. Where thiopurines are not started post-operatively, it was suggested that colonoscopy 1 year after surgery might influence subsequent decision making regarding the use of disease-modifying agents. Decisions should reflect individual risk/benefit considerations.

Question 4 Presented by Professor Murray Barclay

What is the best dosing strategy for immunosuppressives in Crohn's disease, in terms of: starting and maximum doses, duration, dose escalation/de-escalation (when? rate?), which immunosuppressive first?

NZ Modified Answer

Recommended initial dose strategies are either a gradual dose increase starting with 50mg of azathioprine (25mg of 6-mercaptopurine) or full-dose therapy with prior determination of thiopurine methyltransferase activity/genotype. (1b)
Consensus agreement 88%: Mean endorsement 7.4

Assuming normal thiopurine methyl transferase activity, the most effective doses appear to be 2-3 mg/kg for azathioprine and 1-1.5 mg/kg for 6-mercaptopurine administered orally, based on reported clinical trials. There is no evidence to support dose de-escalation. (1b)
Consensus agreement 100%: Mean endorsement 8.5

For methotrexate, the dosing strategy should be 25 mg per week intramuscularly for ~~8-12 weeks~~ ***16 weeks***, and 15 mg per week subcutaneously in maintenance. ***While oral methotrexate may be preferred by patients, there is no data to support this use.*** There is no evidence to support dose de-escalation. (1b)
Consensus agreement 100%: Mean endorsement 8.5

Thiopurines are used as ~~Azathioprine is used as a~~ first-line immunosuppressives. ~~as higher response rates were obtained with it compared with 6-mercaptopurine. There is no evidence for the use of methotrexate as a first-line immunosuppressive.~~ ***Methotrexate is an acceptable alternative immunomodulator.*** (1a)
Consensus agreement 88%: Mean endorsement 7.9

Azathioprine or 6-mercaptopurine treatment should be maintained for ***at least 6 years of remission*** ~~several years~~ due to a high relapse rate in patients with Crohn's disease when these drugs are discontinued. (1b)
Consensus agreement 76%: Mean endorsement 6.8

Discussion

Measuring activity of thiopurine methyl transferase (TPMT), a pivotal enzyme in the metabolic pathway of thiopurines, is a reliable and cost-effective way of identifying individuals at high-risk of developing bone marrow suppression on exposure to thiopurine drugs. One in 300 (0.3%) individuals have very low TPMT activity and should not receive thiopurines. A further 11% have intermediate levels that require dose reduction to avoid bone marrow suppression. Thiopurines may also cause bone marrow suppression in an idiosyncratic fashion and haematological monitoring is therefore recommended, irrespective of TPMT activity. As a consequence, while measurement of TPMT is prudent, studies have failed to show a consistent safety benefit and National Bodies have not uniformly recommended the practice. Group discussion revealed that, in New Zealand, financial constraints, in addition to time delays in receiving TPMT results, have led to patchy uptake of TPMT measurement. However, a show of hands indicated that most delegates measure TPMT as part of their thiopurine monitoring practice.

6-thioguanine nucleotide (6TGN; the active metabolite of thiopurines) concentrations >235 pmol/8x10^8 RBC correlate strongly with clinical response to thiopurines in IBD.[16] While monitoring is rare in the UK and Europe (due to limited access to the assay), a show of hands indicated that most delegates measure 6TGN in their clinical practice (although the cost of the assay limits its use). Research from Christchurch reveals that patients on standard doses of thiopurines (2-3 mg/kg AZA with normal TPMT activity or 1-1.5 mg/kg in patients with intermediate TPMT activity) are likely to have optimal levels of 6TGNs. Indeed, patients with normal TPMT activity generally benefit from doses towards the top of the dose range, 3 mg/kg AZA or equivalent.

Dose de-escalation refers to the practice of reducing thiopurine dose from full treatment dose after a period of remission. There is no

evidence to support this practice.

AZA is an imidazole pro-drug that is non-enzymatically converted to 6-MP. The released imidazole moiety contributes to the adverse effects of the thiopurines including GI disturbance and hypersensitivity, and 6-MP is therefore better tolerated; 50% of patients intolerant of AZA will tolerate 6-MP therapy. Although AZA is more thoroughly investigated in IBD, AZA and 6-MP appear to have equal efficacy[17,18] and either drug may be considered an appropriate first-line immunomodulator.

Few studies have investigated the use of MTX in CD. Cochrane meta-analysis has, however, confirmed the usefulness of MTX for both the induction and maintainance of remission, and found no significant difference in effect between MTX and the thiopurines.[19] While the group could find no evidence that either AZA or MTX should be used preferentially, the undesirable risks of MTX in our young, often female patient population, in addition to historical prerogatives, persuaded the group to retain AZA as the first-line agent of choice, accepting that MTX is a reasonable alternative. In some situations, the first-line use of MTX would be preferred, for example in patients with very low TPMT activity. A show of hands revealed that most delegates used a weekly dose of 25mg SC for the first 16 weeks of MTX therapy, followed by 15mg either SC or orally for maintenance of remission. Of particular note, none of the studies that used oral MTX for the treatment of CD showed benefit, and failure of oral MTX should prompt a change to parenteral administration rather than dismissal of this useful drug.

Disappointingly, while immunomodulators are effective in maintaining remission, a meta-analysis has demonstrated that on their cessation, 50% of patients will suffer disease relapse within 5 years.[20] In this meta-analysis, the median duration of disease remission prior to drug withdrawal was 6 years. Immunomodulators therefore remain effective in maintaining remission despite prolonged use and, putting safety concerns aside (discussed in Questions 6 & 9), it would seem reasonable for patients to remain under treatment for at least 6 years before considering drug withdrawal.

Question 5 (Part 1) Presented by Dr John Wyeth

How should the efficacy of a treatment be monitored clinically and biologically? What is the definition of treatment failure? When should the effect of treatment be evaluated? Should mucosal healing be assessed?

NZ Modified Answer

Remission of signs and symptoms is the most widely clinically accepted endpoint for treatment efficacy. The Crohn's Disease Activity Index (CDAI) and Harvey Bradshaw Index are accepted tools for quantification of efficacy in clinical trials. However, ~~their use~~ ***the use of CDAI*** outside this environment is limited by its cumbersome nature. (5)
Consensus agreement 94%: Mean endorsement 7.9 (Second Vote)

Indirect biomarkers of treatment efficacy include:

- Elevated serum C-reactive protein correlates well with disease relapse and mucosal ~~healing~~ ***inflammation***. (2b)
  Consensus agreement 94%: Mean endorsement 7.8
- Faecal calprotectin below the cut-off level of the individual test (predictive of mucosal healing and reduced relapse in Crohn's disease). (4)
  Consensus agreement 88%: Mean endorsement 7.9

The use of azathioprine metabolites and trough infliximab levels may help management decisions and more accurately identify non-responders. (4)
Consensus agreement 94%: Mean endorsement 8.1

For treatment with thiopurines or methotrexate, clinical response should be assessed after ~~3 months~~ ***a minimum of 4 months.*** However, if mucosal healing is to be assessed, this should be performed ~~between 6-12 months~~ ***after 6 months.*** (4)
Consensus agreement 100%: Mean endorsement 8.1

For treatment with biological agents, clinical response should be assessed between 6-14 weeks. (1a)
Consensus agreement 94%: Mean endorsement 8.1

Patients failing to respond symptomatically after adequate therapy with thiopurines or methotrexate for at least ~~3-6 months~~ ***4-6 months***, or with a biologic for at least 6-14 weeks, constitute a treatment failure. (4; thiopurines and methotrexate), (1a; biologics)
Consensus agreement 100%: Mean endorsement 8.4

Discussion

Scores of disease activity are necessary for clinical trials where a standardised and objective measure of disease severity or response is required. Despite widespread use for this purpose, the most commonly used score, the Crohn's Disease Acitivity Index (CDAI) fails to distinguish between functional and inflammatory activity and correlates poorly with objective markers of disease remission such as mucosal healing.[21] The value of severity scores to guide clinical practice has never been tested and would be fraught with difficulty. In contrast to the cumbersome CDAI, however, delegates agreed that the simpler Harvey Bradshaw Index could be used in routine clinical practice to gather clinical information in a structured manner, while facilitating retrospective or prospective clinical research.

Several biomarkers have proven value in the indirect assessment of disease activity. In particular, a raised C-reactive protein (CRP) correlates well with active disease (although a normal CRP fails to predict mucosal healing, particularly in the small bowel). Furthermore, elevated CRP predicts subsequent response to biological agents.[22] Faecal calprotectin has established use in distinguishing organic from functional gastrointestinal disease, and quiescent from active inflammatory bowel disease.[23]

Although IFX concentrations cannot be measured in New Zealand, delegates agreed that the published literature indicates a role for this, along with human anti-chimeric antibodies in guiding management decisions.

A Cochrane review of the use of immunomodulator therapy in CD found peak response (among those studies that reported it) to occur from 9 weeks to greater than 26 weeks of therapy.[18] Analysis revealed peak response was reached at >17 weeks of therapy and it was concluded therefore that 17 weeks (approximately 4 months) should be the minimum period of treatment before assessing clinical response. Regarding biologic therapy, clinical trials have assessed clinical response between 6 and 14 weeks.

Question 5 (Part 2) Presented by Dr John Wyeth

Should mucosal healing be assessed?

NZ Modified Answer

~~Achievement of~~ Mucosal healing in Crohn's disease ***is associated with*** ~~leads to~~ prolonged steroid-free remission, fewer abdominal surgeries and may reduce hospitalisations. (2b; remission), (4; surgery), (2b; hospitalisation)
Consensus agreement 100%: Mean endorsement 8.6

There is good evidence to suggest that azathioprine, infliximab and adalimumab are effective at healing the colonic mucosa completely. (2b)
Consensus agreement 100%: Mean endorsement 8.7

Early combined ***azathioprine and infliximab therapy*** ~~immunosuppressive therapy~~ in moderately active Crohn's disease is superior to ***monotherapy*** ~~standard therapy~~ in establishing mucosal healing ***in patients naive to these agents.*** (2b)
Consensus agreement 100%: Mean endorsement 8.5

Methotrexate and certolizumab are also capable of mucosal healing, although the evidence base is less firm. (4; methotrexate), (3b; certolizumab)
Consensus agreement 94%: Mean endorsement 8.0

There is currently insufficient evidence to recommend the routine assessment of mucosal healing in the absence of a clinical indication. Non-invasive markers such as C-reactive protein, and in particular faecal calprotectin, may offer realistic alternatives to endoscopy for the assessment of mucosal healing. (5)
Consensus agreement 94%: Mean endorsement 8.1

Discussion

There was unanimous agreement that the published evidence demonstrates mucosal healing (for which there is no validated definition) to be associated with reduced disease progression in Crohn's disease. While mucosal healing and so called 'Deep Remission' (the combination of mucosal healing with symptom resolution) has become the Holy Grail of treatment outcome, delegates cautioned against the pursuit of mucosal healing as the only valuable clinical endpoint. Furthermore, delegates were reluctant to attribute mucosal healing solely to the effect of aggressive combined immunosuppressive therapy, suggesting that for a subgroup, mucosal healing reflects the predestined natural history of their disease.

Clinical remission does not correlate with mucosal healing. Despite this, and consistent with the views expressed above, the group agreed that invasive endoscopic examination to routinely assess for mucosal healing in the absence of a clinical indication was not warranted. In this setting, non-invasive measures of disease activity such as CRP or faecal calprotectin should be used as surrogates.

Question 6 Presented by Dr David Rowbotham

If azathioprine and a biologic are given in combination, should any of the treatment be stopped? Which treatment should be stopped to achieve the smallest reduction in efficacy? When should that treatment be stopped?

NZ Modified Answer

In patients with moderately active Crohn's disease naive to immunosuppressive therapy, the combination of ~~an immunosuppressive~~ ***azathioprine*** with infliximab improves rates of steroid-free remission up to 1 year after commencement of therapy. (1b)
Consensus agreement 94%: Mean endorsement 8.0

In patients ~~refractory to immunosuppressive~~ ***in remission on combination immunomodulator/infliximab*** therapy, continuation of ~~that therapy~~ ***the immunomodulator*** in conjunction with the biologic offers no clinical benefit up to 2 years. (1b)
Consensus agreement 100%: Mean endorsement 8.1

If the immunomodulator is to be continued in conjunction with a biologic, then the ***ongoing use of the immunomodulator*** ~~immunosuppressive may be discontinued~~ ***should be reconsidered*** after 6 months. ~~However, this decision must be individualized.~~ (4)
Consensus agreement 100%: Mean endorsement 7.6 (Second Vote)

It is unclear if ***the addition of biologic to azathioprine confers*** ~~patients on a long-term combination of azathioprine and a biologic have~~ an increased risk of opportunistic infection or malignancy. (5)
Consensus agreement 100%: Mean endorsement 8.0

There is a small potential risk of hepatosplenic T-cell lymphoma in young males with Crohn's disease being treated with a combination of azathioprine and ~~infliximab~~ ***anti-TNF agents.*** (4)
Consensus agreement 94%: Mean endorsement 8.1

Discussion

The episodic use of biological agents (standard practice when IFX was first introduced to the clinical arena) contributes to their immunogenicity, resulting in the formation of neutralising antibodies, allergic infusion reactions and loss of response. The co-prescription of immunomodulators in this setting was found to limit antibody formation and prolong the useful life of biological agents. Standard practice has changed, and with regular maintenance dosing, immunogenicity is reduced, resulting in a lower incidence of neutralising antibodies and a more durable response. This change in practice, together with the small, but clear risk of hepato-splenic T-cell lymphoma in patients on combined anti-TNF/AZA therapy, requires the blanket co-prescription of immunomodulators with biologics to be reconsidered. In patients in remission who have received combination therapy with an immunomodulator and biologic for at least 6 months, withdrawal of the immunomodulator does not appear to influence remission rates in the subsequent 2 years (although CRP and the presence of neutralising antibodies was higher in this group).[24] In immunomodulator and biological naive patients, however, the combination of IFX and AZA resulted in the highest rates of remission and mucosal healing when compared with either drug alone. The added benefit of giving these drugs in combination is not thought to be derived solely from an effect on immunogenicity. In this setting, whether AZA could be withdrawn without detriment after 6 months of remission has not been addressed. Cessation of therapy after 2 years of treatment with a biological, however, leads to relapse in 50-60% of patients. Similar studies have not been performed with adalimumab or certolizumab. In the d'Haens et al "top down vs step up" study, early combined immunosuppression, when compared with standard sequential introduction of CS, immunomodulators and biologics resulted in a lower requirement for biologics after 2 years.[25]

Investigating the clinical factors that are associated with opportunistic infection in IBD patients, Toruner et al identified 100 consecutive patients with opportunistic infection and matched each with two IBD patients with no such history.[2] In univariate analysis the use of CS, AZA or IFX individually conferred similar risk (OR 3.4, 3.1 and 4.4, respectively). Multivariate analysis indicated that the use of any one of these drugs yielded an OR of 2.9, whereas use of two or three of these drugs yielded an OR of 14.5 for opportunistic infections. Risk was greater for those >50 years of age compared with those aged <24 years, and was greatest when AZA and CS were used in combination (OR 17.5).[2] Data from neither SONIC nor the Toruner study could demonstrate increased opportunistic infectious complications for the combination of AZA and IFX compared with AZA alone (SONIC; incidence of severe infection 3.9%, 4.9% and 5.6% with combination therapy, IFX monotherapy and AZA monotherapy, respectively).

If AZA and a biologic are given in combination, should any of the treatment be stopped? The group agreed that it would be reasonable to consider stopping one agent, probably AZA (given the better response to IFX monotherapy and risk of loss of response associated with episodic treatment with biologics). Delegates recognised that decisions are likely to be coloured by clinical experience of adverse events, and agreed that decisions need to be made on an individual basis. Delegates indicated that their current standard practice is to add a biologic to patients failing on immunomodulator therapy and then reconsider the need for the immunomodulator at a later date.

Question 7 Presented by Dr David Rowbotham

If the immunosuppressive does not work, what should the approach be? Increase the dosage? Add steroids? Change the immunosuppressive? Move to a biologic?

NZ Modified Answer

Optimisation of thiopurine therapy should always be considered ~~if underdosing is suspected on a dose/weight basis~~. (1a)
Consensus agreement 100%: Mean endorsement 8.8

Anti-TNF agents should be ~~the first consideration~~ ***considered*** in patients who have been on immunosuppressives and have lost response. (1b)
Consensus agreement 100%: Mean endorsement 7.8 (Second Vote)

Adding steroids may be necessary in the short term as a ***bridging strategy***, but they are not recommended for long-term use (patients should be weaned off steroids). (4)
Consensus agreement 94%: Mean endorsement 7.6

In the setting of intolerance or side effects to ~~purine~~ azathioprine ~~metabolite immunosuppressives,~~ other immunosuppressives may be considered ***including***; ~~Alternative immunosuppressives include~~ 6-mercaptopurine, methotrexate, ***or in limited settings*** tacrolimus, ***mycophenolate*** and 6-thioguanine. ~~(in limited settings only)~~. (4)
Consensus agreement 94%: Mean endorsement 8.0

Discussion

The group unanimously recommended optimising established immunomodulator therapy (either with or without metabolite monitoring) as the first consideration in patients experiencing a flare of disease (Question 4). In this setting, CS are a useful stop gap to bridge the period between dose escalation and clinical response. Where immunomodulator dose is already thought to be optimal, the medical alternatives are either to change to a different immunomodulator or add a biologic. There is no direct evidence to support one over another, however, bearing in mind the relatively higher risk associated with combined CS/immunomodulator therapy, use of rapidly effective biologics (that negate the need for CS induction) may have risk/benefit advantages. Budesonide has not been evaluated in the setting of immunomodulator failure, but may be a low-risk alternative to systemic CS in some situations. Delegates reported the most common approach in this situation to be to increase the thiopurine dose and use a course of CS to provide short-term symptomatic relief.

Reviewing the evidence for the use of alternative immunosuppresants (tacrolimus, cyclosporine A, mycophenolate mofetil and 6TGN) was beyond the scope of this report and was only discussed briefly at the IBD AHEAD meeting. It was the general consensus that where their use is being considered, discussion with an IBD specialist knowledgeable in their use is advised.

Question 8 Presented by Dr John Wyeth

If a patient experiences flare-ups when receiving immunosuppressives or a biologic, should corticosteroids be added?

NZ Modified Answer

Patients ***relapsing*** on ~~failing~~ immunomodulator ~~immunosuppressive~~ therapy can be started on corticosteroids to help induce remission when ~~transitioning~~ ***bridging*** to another ~~immunosuppressive~~ ***immunomodulator*** ~~or biologic agent~~. Biologics, however, should be considered as both induction and maintenance agents and transition is not usually necessary. (1b)
Consensus agreement 93%: Mean endorsement 7.6

When started, corticosteroid dose should be ~~rapidly~~ tapered over a period of weeks to avoid long-term exposure. (3)
Consensus agreement 93%: Mean endorsement 8.1

Given their significant side-effect profile, use of corticosteroids should be limited or avoided where possible. (3)
Consensus agreement 94%: Mean endorsement 8.5

If a patient loses response to a biologic, optimisation of therapy should be considered before starting steroids. (3)
Consensus agreement 93%: Mean endorsement 8.0

For discussion see Questions 1, 6 & 7

Question 9 Presented by Dr Michael Schultz

What are the risks of cancers (all kinds) and infections associated with the short-, mid- and long-term use of immunosuppressives and corticosteroids?

NZ Modified Answer

Although the overall cancer risk does not seem to be increased in patients on steroids or immunosuppressives, thiopurines increase the risk of lymphoproliferative disorders and non-melanoma skin cancers in IBD patients. (2b)
Consensus agreement 100%: Mean endorsement 8.3

Steroids and immunomodulators are associated with an increased risk of infection. (2b)
Consensus agreement 100%: Mean endorsement 8.6

The risk of infection in patients with IBD increases with the number of ~~anti-inflammatory~~ ***immunosuppressive*** agents that are used concomitantly. (3b)
Consensus agreement 100%: Mean endorsement 8.8

The concomitant use of immunosuppressive agents and biologics should be minimised, especially in adolescents and young adults. (5)
(This statement was disagreed by majority)
Consensus disagreement 87%: Mean endorsement 3.0

Discussion (see also Discussion, Question 6)

Concerns over the long-term risk of thiopurine drugs and, in particular, the risk of lymphoma, has for a long time dominated discussion about the safe duration of thiopurine treatment. Studies have variably reported the following; no increased risk of lymphoma, increased risk associated with CD but not related to medication use, and finally, a small but definite increased risk associated with thiopurine use.[26] Beaugerie's convincing 2009 paper describes a multi-centre cohort of more than 19000 patients with IBD; 5867 of whom were receiving thiopurines and a further 2809 who had discontinued use.[27] Multivariate-adjusted hazard ratio for lymphoproliferative disorders between patients receiving thiopurines and those who had never received the drugs was 5.28 (2.01-13.9, $p = 0.0007$), with incidence rates of lymphoproliferative disorders of 0.9 per 1000 patient-years for those receiving thiopurines, 0.2 per 1000 patient-years for those who had discontinued use and 0.26 per 1000 patient-years in those who had never received the drugs. Risk of lymphoproliferative disease was associated with thiopurine use, old age, male sex and duration of IBD. Despite these findings, the reported

increased risk of non-melanoma skin cancer in IBD patients receiving immunomodulators and concern based on data from the transplant literature, studies have found no association between thiopurine use and overall cancer risk in IBD.[26, 28] IFX also appears safe in this regard.[29]

Hepatospenic T-cell lymphoma (HSTCL) is a rare, but invariably fatal form of peripheral T-cell lymphoma which has been associated with the use of thiopurines, often in combination with anti-TNF biologicals in CD. There are 28 recorded cases in the literature, only one of which has achieved remission. Cases are typically young males.[30] Concern over HSTCL has had a significant influence on willingness to co-prescribe thiopurines with biological agents. The effectiveness of combination therapy is, however, undeniable, while the risk of lymphoma is small and of HSTCL, vanishing. In this context, delegates voted unanimously that excessive attempts to minimise immunosuppressive use in young patients (who by definition have the greatest risk of future morbidity) is unwarranted. This statement does not, however, detract from the responsibility of physicians to ensure that immunosuppressant use is carefully considered, counselled for, appropriate to the stage and severity of disease, and carefully monitored.

Question 10 Presented by Dr Michael Schultz

What is the optimal safety monitoring (clinical, laboratory, radiological) of patients receiving immunosuppressives or corticosteroids? How often?

NZ Modified Answer

Thiopurine therapy ~~Immunosuppressive therapy~~ is associated with myelosuppression. Patients with low thiopurine methyltransferase (TPMT) activity are at increased risk of developing severe myelosuppression. However, 73% of patients with severe bone marrow suppression do not carry a TPMT mutation. (3b-5)

Consensus agreement 100%: Mean endorsement 8.7

~~As TPMT analysis may predict 90% of life threatening episodes and 69% of severe and moferate episodes of neutropenia~~ Measuring TPMT activity prior to starting thiopurines is a cost-effective way of identifying patients at high-risk of severe haematological complications. (5)

Consensus agreement 95%: Mean endorsement 8.1

All patients receiving thiopurines or methotrexate need regular monitoring of their full blood count and liver tests. ~~In patients receiving methotrexate, measurement of full blood count and liver function tests are advisable before and within 4 weeks of starting therapy, then monthly to every 3 months~~ (5)

Consensus agreement 100%: Mean endorsement 8.7

Nodular regenerative hyperplasia is a rare but potentially severe complication of azathioprine in patients with IBD. Clinicians should be aware of this complication and should monitor liver function tests and platelet counts ~~closely~~ ***regularly***. (5)

Consensus agreement 94%: Mean endorsement 8.4

~~Clinical~~ Monitoring of patients receiving ~~high dose~~ steroids is recommended, and doses should be tapered ***where clinically appropriate***. ~~However, there is no evidence to support any particular method of monitoring.~~ (5)

Consensus agreement 93%: Mean endorsement 8.6

For discussion see Questions 3 & 4

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