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Best practices on immunomodulators and biological agents for Ulcerative colitis and Crohn's disease in Asia

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Abstract

The Asia Pacific Working Group on Inflammatory Bowel Disease (IBD) was established in Cebu, Philippines, under the auspices of the Asian Pacific Association of Gastroenterology (APAGE) with the goal of improving IBD care in Asia. This consensus is carried out in collaboration with Asian Organization for Crohn's and Colitis (AOCC).

With biological agents and biosimilars becoming more established, it is necessary to conduct a review on existing literature and establish a consensus on when and how to introduce biological agents and biosimilars in the conjunction with conventional treatments for ulcerative colitis (UC) and Crohn's disease (CD) in Asia. These statements also address how pharmacogenetics influence the treatments of UC and CD and provide guidance on response monitoring and strategies to restore loss of response. Finally, the review includes statements on how to manage treatment alongside possible Hepatitis B and tuberculosis infections, both common in Asia. These statements have been prepared and voted upon by members of IBD workgroup employing the modified Delphi process. These statements do not intend to be all-encompassing and future revisions are likely as new data continue to emerge.

Keywords

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, biosimilar, infliximab, adalimumab

Introduction

The prevalence of inflammatory bowel disease (IBD) in Asia, whilst not having achieved the same prevalence as in countries of the western hemisphere, is on the rise. The Asia-Pacific Working group on IBD previously published two review papers that addressed the definition, diagnosis, epidemiology[1,2] as well as the management of IBD. Corticosteroids and mesalazine remain important agents used in the induction of remission in IBD throughout Asia. Given the endemicity of hepatitis and tuberculosis in Asia, the use of immunomodulators and biological agents requires considerations not taken into account in the rest of the world.

Immunomodulators, which include methotrexate and the thiopurines modify the immune system with the aim of inducing and maintaining remission. Their effects are systemic and not as targeted as the biological agents. The thiopurines are generally slow acting but there is greater experience in their use. Biological agents are a class of drugs produced by living organisms such as bacteria or mammalian cells in culture. These drugs consist of large and complex molecules and are often protein-based. They are relatively new in many parts of Asia, and hence, more guidance is required in their use as monotherapy agents or in combination therapy with immunomodulators. Biological agents also provide a more targeted approach to reducing inflammation in the form of monoclonal antibodies against tumor necrosis factor-alpha (anti-TNFs), interleukins and integrins. However, due to the high cost of these drugs, there are constraints in making them widely accessible in Asia.

This paper will review how immunomodulators can be coupled with biological agents as a treatment protocol for IBD. The paper will cover indications for initiation of such therapy,

disease monitoring, individualized dosing of these drugs and exit strategies. Pharmacogenetics or precision medicine have helped optimized the drug armamentarium for IBD. For patients being considered for thiopurines, thiopurine methyltransferase(TPMT) polymorphisms, while important for Western populations, may not be as relevant in Asia. However, nucleoside diphosphate linked moiety X-type motif 15 (NUDT15) genotyping is encouraged, where available, prior to initiation of azathioprine. Further to the Asian context of this review, endemic diseases such as TB and Hepatitis B require special attention prior to treatment. Rigorous screening protocols and the use of prophylaxis measures, where appropriate, will be addressed.

Methods

A modified Delphi process[3] was adopted to develop the consensus statements according to their clinical importance within the Asia-Pacific region. A steering committee (CJO, IH, RB, RWL, CSW, SCN, PP, VA) generated a list of statements and circulated it electronically to Consensus Group members. These statements were presented to the Consensus Group panel for discussion, revision, and voting. A password-secured website was populated with the relevant literature assembled by the steering committee. A systematic literature review was conducted to identify and grade the available evidence to support each statement. The literature search was conducted in the English language publications indexed in the MEDLINE, EMBASE, and the Cochrane Trials Registry databases, and limited to those in human subjects. Regional and international consensus statements and guidelines on IBD were examined. Relevant literature from the Asia-Pacific region was of particular interest.

The categorization of evidence, classification of recommendation, and voting schema were according to the Canadian Task Force on the Periodic Health Examination (Table 1).[4] Consensus was achieved when 80% or more of votes were either accepted "completely" or "with some reservation." A statement was refuted when 80% or more of voting members rejected a statement "completely" or "with some reservation." Every statement was then graded to indicate the level of evidence available and the strength of recommendation.

Membership of the consensus group. Voting members of the Consensus Group were selected using the following criteria:

1. Demonstration of knowledge and expertise in IBD through publication/research or participation in national or regional guideline development.
2. Geographical representation of the Asia-Pacific countries.
3. Diversity of views and expertise in healthcare system (including colorectal surgeon, pathologist, pharmacist, nurse practitioners). Voting was limited, however, to clinicians.

Representative countries included Malaysia, Thailand, Sri Lanka, India, China, Hong Kong, Taiwan, Philippines, Indonesia, Australia, New Zealand, Japan, South Korea and Singapore.

Voting, Delphi process, and general organization of the consensus.

Voting was conducted anonymously at all times. The first vote was conducted by the entire Consensus Group electronically by email. Relevant literature was then made available on a secured website for review by all voters, and a second round of voting was undertaken, during which members could modify their first-round selections, if required. A third and final vote was held thereafter during a face-to-face meeting. Statements that could not

reach consensus were discussed and either modified or rejected. Each statement was graded to indicate the level of evidence available and the strength of recommendation by using the Canadian Task Force Guidelines on the Periodic Health Examination.[4] Improvement to the wording of the statements was permitted following an open discussion. The full Consensus Group meeting was held in August 2017 in Penang, Malaysia. Representatives attended from Asia-Pacific countries that included Australia, Hong Kong, India, China, South Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand.

Results

Part A: Biological Therapy – Who to consider for biological agents and when to start?

Statement 1:

Biological therapy (Anti-TNFs, anti-integrins, anti-IL12/23) should be initiated for the treatment of moderate-to-severe Crohn's disease (CD). This includes corticosteroid or immunosuppressant refractory/ intolerant disease and corticosteroid dependence.

Level of agreement: (a) 100%, (b) 0%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: I

Classification of recommendation: A

Biological therapy can be initiated in moderate to severe inflammatory active disease if conventional therapy fails or if it is not tolerated.[5] The conventional therapy for moderate to severe luminal CD include mesalazines and corticosteroids as the first line therapy. Immunomodulators are commenced as corticosteroid-sparing agents in case of recurrent relapses, corticosteroid dependence or corticosteroid refractory states. Several studies have provided evidence that the use of biological agents with- or without immunomodulators in

moderate to severe CD can reduce inflammation and flares. The use of biological agents promotes mucosal healing, as well as lower the rates of hospitalization and surgery.[6–8] In an European multicentre trial, histological remission and mucosal healing were demonstrated with infliximab in CD.[9] Lichtenstein *et al.* reported that in patients enrolled in the ACCENT II trial, infliximab reduced hospitalizations, surgeries, and procedures.[7] The EXTEND trial showed that adalimumab effectively induced and maintained mucosal healing.[10]

Anti-TNFs have been extensively evaluated for the induction of remission and maintenance in CD in several randomized control trials and meta-analyses. Infliximab was the first biological agent and has the maximum published data with regards to the use of biological agents in CD. The ACCENT 1 trial demonstrated the efficacy of infliximab as a maintenance therapy in patients who responded to an initial dose of infliximab and discontinued corticosteroids whilst maintaining prolonged remission.[11] In the CHARM trial, adalimumab was found to be effective in maintaining remission in moderate to severe CD through to 56 weeks.[12] The Precise 1 and Precise 2 trials demonstrated that certolizumab pegol was able to induce and maintained remission in moderate to severe CD.[13,14] However, it needs to be mentioned that the patient cohorts in these studies have been heterogeneous, including patients with both corticosteroid naïve and corticosteroid dependent or resistant disease, and the latter studies included patients that had failed prior anti-TNF therapy.[15]

The anti-integrin antibody, vedolizumab has shown efficacy in the management of moderate to severe CD in both anti-TNF naïve subjects and those that had failed anti-TNF treatment in the GEMINI II[16] and GEMINI III studies.[17] Natalizumab, an earlier anti-integrin antibody, is not widely used due to the increased risk of progressive multifocal

leukoencephalopathy.[17,18] Ustekinumab is a monoclonal antibody directed against the p40 subunit of interleukin 12 and interleukin 23. It effectively induces and maintains remission in moderate to severe luminal CD including those who had failed anti-TNFs in the pivotal UNITI I/II and IM-UNITI clinical trials.[19] Currently there is no head-to-head data comparing the currently available biologic therapies. The choice of biological therapy, therefore, should take into consideration patient and disease characteristics, reimbursement policies/cost, risk for adverse effects, presence of extra-intestinal manifestations, possibility of pregnancy, as well as patient's preference in terms of the route of administration.

Statement 2:

Although early use of biological therapy has been shown to improve clinical outcome, the top down approach cannot be recommended in all patients with active CD. An accelerated step up to biologic therapy can be suggested after consideration of high risk factors and predictors of poor outcome.

Level of agreement: (a) 66.67%, (b) 33.33%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: I

Classification of recommendation: A

The traditional therapeutic approach is a step-up treatment strategy which consists of initiating biologic therapy only after conventional therapy has failed to control the disease. However, this approach has raised concerns that delaying biologic therapy may result in irreversible intestinal strictures and fistulizing disease. Accordingly, a top-down treatment strategy with the early use of biological agents was suggested.[20,21] The top-down approach has been shown to be more effective in maintaining remission, decreasing the rate of relapse, reducing the administration of corticosteroids, preventing the occurrence of

complications and minimizing surgeries in the long term as well as improving the quality of life.[20] However, there are other factors that need to be considered for the top-down approach, particularly within Asia.

In many Asian countries, where there is a high prevalence of latent TB, the use of anti-TNFs with top-down approach may be risky. Navara *et al.* assessed the risk of TB in patients treated with anti-TNF agents in Asia and reported a substantially higher number of patients at risk compared to Western Europe and North America.[22] In addition to TB, other opportunistic infections and malignancy remain a major concern especially when biological agents are introduced early and for a prolonged duration. Additionally, top-down treatment may not be cost-effective if this approach is considered in every patient with CD, especially in countries where most of the people are uninsured.[23] The proportion of CD patients under treatment with biological agents in Asian countries differ markedly and is as high as 30-40% in Japan, where the government pays for all the expenses for IBD, down to 1% in India, where patients have to pay for biological agents themselves.[23] Primary top-down therapy also risks over-treatment. Lin *et al.*, and Kim *et al.*, reported that as high as 30% of patients might have been over-treated with this approach.[24,20] Identification of subgroups that would benefit the top-down therapeutic approach that maximizes the treatment benefit-risk profile is required.[15,24]

The alternative accelerated step-up approach is one where biological agents are introduced early in patients with high risk factors for failure with conventional treatments to permit better clinical outcomes.[25] Various studies have been published to identify predictors for poor outcomes in CD so as to categorise patients in terms of risk. Beaugerie *et al.* reported

that for patients below the age of 40 years, the presence of perianal disease, and the initial requirement of corticosteroids are factors predictive of subsequent 5-year disabling course.[26] Sands *et al.* reported that the use of corticosteroids in the first 6 months of diagnosis was associated with four-fold increased risk of surgery.[27] Other clinical markers include stricturing or penetrating disease behaviour, extensive disease, small bowel disease and perianal disease.[28,29] Smoking was associated with poorer outcomes such as the development of strictures, fistulae, increased risk for surgery and the need for corticosteroids and/ or immunomodulators.[28,30] The presence of risk factors would place the patient in the moderate/ high-risk category, whereas limited anatomic involvement with superficial ulcers, the absence of stricturing/ penetration behaviour, perianal disease/ rectal disease and prior surgical resection would place the patient in a low-risk category.[31]

Risk stratification helps in identifying patients at risk of poor prognosis and guides clinicians in identifying patients who might benefit from early aggressive therapy while at the same time avoiding over treatment in those with mild disease. An Asian study was undertaken by Oh *et al.* which reported that Korean patients with poor prognostic factors treated with anti-TNFs or immunomodulators within 2 years of diagnosis is associated with better clinical outcomes than later treatment. The poor prognostic factors include patients younger than 40 years of age at diagnosis, treated with systemic corticosteroids within 3 months of diagnosis and had a perianal fistula at the time of diagnosis.[32]

Statement 3:

Combination therapy should be considered in patients naïve to biological agents, particularly infliximab, at least for the first six months to one year of therapy but this must be carefully weighed against the risks of infection and malignancy.

Level of agreement: (a) 45.45%, (b) 45.45%, (c) 9.09%, (d) 0%, (e) 0%.

Quality of evidence: II-3

Classification of recommendation: A

Studies have suggested that early combination therapy of infliximab with azathioprine is more efficacious than monotherapy with infliximab in terms of induction of remission and reduction of corticosteroid use.[33,34] The SONIC trial demonstrated the superiority of infliximab combination therapy over monotherapy in CD patients naïve both to thiopurines and biological agents.[34] Similarly, the UC success study, has also shown that infliximab and azathioprine combination therapy is superior to infliximab or azathioprine alone. [35] However, a meta-analysis reported that combination therapy of anti TNF therapy with immunomodulators is not as beneficial compared to monotherapy in inducing or maintaining a clinical response when anti-TNF therapy is added to an existing immunosuppressive regimen.[36] Studies have also failed to show the benefit of combination therapy with adalimumab/immunomodulator as compared to adalimumab monotherapy.[37]

The benefits of combination therapy are reduced immunogenicity, increased serum levels and better efficacy of anti-TNF agents. In addition to reducing immunogenicity, immunosuppressants can reverse anti-drug antibody formation mostly within 12 months.[38,39]

This must be carefully weighed against the risk of infection, especially in Asian countries where the prevalence of TB is high (see statements 27 to 29). Another rare risk is hepatosplenic T-cell lymphoma which has been associated especially with thiopurines.[36] Currently, there is no data available on combination therapies involving non anti-TNF medications. Evidence on the combination therapy of methotrexate with infliximab is limited, however, available data suggest that combination therapy is no more effective than monotherapy with infliximab.[40]

In a study on immunosuppression withdrawal in CD, continued treatment with immunosuppressives beyond 6 months of combination treatment offered no additional benefit over infliximab monotherapy in patients with CD in stable remission. In a randomized control trial, 1–1.25 mg/kg/day azathioprine was as effective as full dose azathionprine in terms of preventing clinical relapse after 1 year in IBD patients on remission on combination therapy. Thus, a low dose immunosuppressant for short duration (6-12 months) is an effective strategy for combination therapy.[41–43]

Statement 4:

Episodic treatment should be avoided to prevent sensitization. However, de-escalation or discontinuation of biologic therapy, may be considered in carefully selected cases.

Level of agreement: (a) 90.00%, (b) 10.00%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II

Classification of recommendation: B

Biological agents are expensive and thus biologic therapy should not be initiated unless one can afford the treatment for at least six to twelve months. For patients who are immunosuppressant resistant or intolerant, treatment, once started, should be prolonged. Single dose or episodic treatment should be strictly avoided as they may lead to antibody-formation resulting in loss of efficacy, increased risk of infusion and possible delayed hypersensitivity reactions. The development of antibodies has been shown to be as high as 30-61% in patients receiving episodic infliximab compared to 7-10% in patients with scheduled infliximab infusions.[15,44] The incidence of anti-drug antibodies was lower in patients with concomitant immunomodulators than in those patients without immunomodulators.[45,11] Sands *et al.* reported that the likelihood of infusion reactions was 2-3 times higher in patients who were positive for antibodies to infliximab than in those who were negative for antibodies or had inconclusive results.[45] ACCENT 1 trial documented the occurrence of infusion reactions in 16% of patients positive for antibodies to infliximab compared to 8% in those without antibodies.[11]

After discontinuation of anti-TNF therapy, relapse rates of 40 and 50% over a 2-year period have been reported by various studies. In many parts of Asia, it is not possible to continue biological therapy indefinitely due to the high cost of therapy or difficult access to infusion centres. Therefore, discontinuation of biological therapy may need to be considered if the patient meets certain criteria.

Factors that that may tip a clinician to consider de-escalation of therapy include older patients, limited disease involvement, little or no treatment delay after early diagnosis and good treatment response to stable therapy. De-escalation can also be considered in

patients with mucosal healing who are in prolonged remission. A history of cancer or serious infections during biologic therapy may preclude the continuation of such therapy. Young patients, the presence of ileal/peri-anal/extensive disease, previous immunomodulator failure/surgery/anti-TNF use and relapsing course are factors that favour the continuation of therapy.[46] Stopping biologics in patients in deep remission (clinical and endoscopic) is associated with a low chance of relapse (STORI Trial).[47] Dose reduction, lengthening interval of therapy and drug re-cycling can be a cost-effective strategy in patients in whom stopping treatment is not feasible.[48–50]

Statement 5:

Biological agents should be used as first-line treatment for complex perianal fistulas in combination with surgical intervention. For simple perianal fistulas, biological agents is recommended if surgical intervention, antibiotics and immunomodulators fail.

Level of agreement: (a) 85%, (b) 15%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: I

Classification of recommendation: A

Perianal fistulas is a significant complication observed in 21-54% of CD. There is strong data for the use of biologic therapy for perianal disease. Antibiotics with or without local drainage (for example, using setons) is usually adequate for simple perianal fistulas without active rectal inflammation. For complex CD-related fistulas, there is limited benefit with thiopurines; corticosteroids are ineffective and may worsen the sepsis.

Biological agents have resulted in a paradigm shift in the management of this CD-related perianal fistulas. The ACCENT II study showed that infliximab at a dose of 5mg/kg at 0, 2 and 6 weeks followed by 8 weekly maintenance for 54 weeks resulted a fistula closure of 36% versus 19% in the placebo group.[45] A recent meta-analysis has confirmed the efficacy of all anti-TNFs (infliximab, adalimumab and certolizumab pegol).[51] Subgroup analysis from the GEMINI II study also showed the benefit of vedolizumab in CD-related perianal fistulas.[52] Currently, there are no head-to-head data comparing the efficacy of the different biological agents. A small retrospective study did not show a significant difference in recurrence between infliximab and adalimumab.[53] The management of perianal fistulas requires a multidisciplinary approach and emerging therapies such as intra-lesional mesenchymal stem cells will further enhance the benefit of biological agents and reduce the rates of proctectomy and permanent stoma.[54]

Statement 6:

Biological therapy is recommended for the treatment of moderate-to-severe UC if conventional therapy fails.

Level of agreement: (a) 95%, (b) 5%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: I

Classification of recommendation: A

The ACT 1 and 2 studies showed the benefit of infliximab for both induction and maintenance of moderate to severe UC.[55] Adalimumab has also been found to be efficacious in UC (ULTRA studies),[56] as has golimumab (PURSUIT studies).[57,58] The GEMINI I study found vedolizumab to be efficacious in the induction and maintenance of remission in

UC.[59] Biological agents, therefore, should be initiated in patients not responding to conventional therapy; which is usually defined as disease that is refractory or intolerant to adequate doses of immunosuppressive therapies such as a thiopurine and methotrexate, corticosteroid dependence (recurrence of symptoms on corticosteroid tapering) or corticosteroid refractory disease.

Statement 7:

Infliximab or cyclosporine A should be considered as rescue therapy in patients with acute severe UC that is non-responsive to intravenous corticosteroids within 3 – 7 days.

Level of agreement: (a) 86%, (b) 14%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: 1

Classification of recommendation: A

A randomized study of corticosteroid-refractory severe UC patients evaluated the effect of infliximab rescue therapy on colectomy avoidance. At 3 months, those randomized to infliximab showed a significantly lower colectomy rate than the placebo group (29% vs 67%) with fewer post-operative complications.[60] Cyclosporine has long been shown as an effective rescue therapy in corticosteroid refractory acute severe colitis.[61] An open labelled study comparing the two drugs did not show any significant difference in outcome[62] and this was confirmed in the CONSTRUCT study.[63] Therefore, the choice of treatment is based on factors such as local availability, cost of therapy and physician preference, whether patients have been unsuccessfully treated with thiopurines previously.[64] Currently there are no data for other biological agents such as adalimumab, golimumab and vedolizumab and the general consensus is that these drugs do not act rapidly enough to be effective in this

setting. Surgery remains a reasonable and cost-effective option, particularly in many parts of Asia.

Statement 8:

Anti-TNFs are the preferred biological therapy for extra-intestinal manifestations of IBD that are severe or unresponsive to conventional treatment.

Level of agreement: (a) 50%, (b) 44%, (c) 6%, (d) 0%, (e) 0%.

Quality of evidence: II

Classification of recommendation: B

Anti-TNFs are approved for many autoimmune conditions such as rheumatoid arthritis and psoriatic arthropathy and their efficacy in extra-intestinal manifestations for IBD, in particular, is well-established. A recently published systemic review has confirmed that anti-TNFs are effective for many of the extra intestinal manifestations including arthropathies, skin manifestations especially pyoderma gangrenosum, ocular manifestations and anaemia.[65] At present, there is minimal data for ustekinumab and vedolizumab. Although a recent study shown that vedolizumab was effective in reducing extra intestinal manifestations associated with intestinal activity,[66] more data is required.

Statement 9:

Anti-integrins and anti-IL-12/23 may be associated with a lower risk of TB.

Level of agreement: (a) 63%, (b) 37%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-2

Classification of recommendation: B

Anti-TNFs are indicated for those who fail conventional therapy but TB reactivation remains a concern in TB endemic countries. Prior to starting an anti-TNF, rigorous testing for the exclusion of TB or latent TB is required.

Vedolizumab, on the other hand, is unlikely to reactivate TB. A review by Colombel *et al.* of 2,830 patients across 6 IBD clinical trials showed only 4 cases of TB.[67] The real world GETAID study did not show any cases of TB in 173 CD and 121 UC cases in 54 week follow up.[68] Similarly, 94 CD and 42 UC patients from USA treated for either UC or CD did not show any TB reactivation after 1 year.[69]

Ustekinumab also have decreased sepsis risk and lower potential for TB reactivation than anti-TNFs. In the Psoriasis Longitudinal Assessment and Registry PSOLAR study involving 12,093 patients and 40,388 Patient Years (PY), overall incidence rates were 0.68/100PY for malignancy, 1.60/100PY for serious infection, and 0.46/100PY for mortality. Unadjusted rates of serious infection for infliximab (2.91/100PY) and other biological agents (1.91/100PY) were numerically higher compared with ustekinumab (0.93/100PY).[70] Tsai, in a review of 3,172 plaque psoriasis patients across five Phase III trial of ustekinumab, showed no reactivation of LTBI reactivation was observed in patients receiving continuous isoniazid prophylaxis for LTBI.[71] Papp, in an analysis of 2014 PSOLAR data did not identify any serious

infection with ustekinumab.[72] In the psoriatic arthritis studies PSUMMIT I and PSUMMIT II, McInnes[73] and Ritchlin[74] reported on 615 and 312 subjects respectively. No cases of TB were reported in the follow up period of 52 weeks in PSUMMIT I and 60 weeks in PSUMMIT II.[73,74] There are isolated case reports documenting TB in patients treated with ustekinumab. These involved a case of peritoneal TB and peripheral lymph node reactivation of TB in patients with psoriasis treated with ustekinumab.[75,76] The relative safety of ustekinumab was again noted when assessed in 1,407 adult patients with moderate to severely active CD in 3 randomized, double-blind, placebo-controlled, parallel-group, multicentre, phase 3 studies (2 induction trials, UNITI-1, UNITI-2; 1 maintenance trial, IMUNITI).

Part B: Biosimilars

Statement 10:

Currently approved biosimilars are as safe and effective as reference products and can be used as induction and maintenance therapy for both CD and UC.

Level of agreement: (a) 50%, (b) 44%, (c) 6%, (d) 0%, (e) 0%.

Quality of evidence: II-2

Classification of recommendation: B

A biosimilar medicinal product is an almost an identical copy of an original licensed "reference" biological agent. Biosimilars in IBD may reduce drug acquisition cost and increase cost-effectiveness and increase capacity for their use. Given the complexity of the structure of monoclonal antibodies, minor structural differences of the drug are unavoidable as the manufacturing process cannot be absolutely controlled. These minor structural changes may theoretically result in changes to the drug's immunogenicity, which

may then change its efficacy and safety particularly following one- or multiple switches from the originator produce or from different biosimilars.[77,78] As such, biosimilars are not generic drugs because they are not identical to the originator biological agent.

Cohen *et al.* conducted a systematic review of switching reference medicines to biosimilars.[79] 90 studies were identified involving seven agents that treated 14 disease indications, and enrolled a total of 14,225 individuals. Most of these studies showed that there were no differences in terms of safety, efficacy or immunogenicity after switching patients to biosimilars. These data addressed concerns over immunogenicity, efficacy and safety when switching from an innovator to a biosimilar biological agent. Prospective and retrospective IBD-specific data showed that switching to biosimilars (mostly CT-P13, also known as Inflectra, Remsima and infliximab-dyyb, the first biosimilar monoclonal antibody) made no significant differences in efficacy, safety and immunogenicity.[79] The PROSIT-BIO cohort: a prospective observational study of patients with IBD treated with CT-P13 included 313 CD and 234 UC patients. Of these, 97 patients who were on infliximab were switched directly to CT-P13 and comparable outcomes were observed.[80] Schmitz *et al.* studied a cohort of 133 IBD patients (64% CD, 36% UC) on the infliximab innovator, Remicade who were switched to infliximab biosimilar, Inflectra. No differences in drug levels and disease activity between infliximab innovator and biosimilar were found, indicating that these biosimilars were safe and effective.[81] A post-marketing study from Korea included 176 patients with active moderate-to-severe CD, fistulizing CD, or moderate-to-severe ulcerative colitis (UC) treated with biosimilar infliximab (CT-P13) and followed for 30 weeks and found that CT-P13 was well tolerated and efficacious in patients with IBD.[82]

The FDA has already approved 4 biosimilars: infliximab-dyyb (Inflectra, Celltrion) and infliximab-abda (Renflexis, Merck), which are biosimilars to infliximab, as well as adalimumab-atto (Amjevita, Amgen) and adalimumab-adbm (Cyltezo, Boehringer Ingelheim), which are biosimilars to adalimumab (Humira, AbbVie). The FDA has accepted the concept of extrapolation of indication.

Biosimilar should be prescribed by brand name as well as by International Non-proprietary Name. It is the responsibility of healthcare professionals to make sure that there is shared decision making by giving all the relevant information and confirm informed consent before initiating biosimilar administration, taking into consideration the preference of the patient. Since biosimilars are essentially the same molecule, switching to a biosimilar will not prevent immunogenicity to the reference medicine which lead to loss of response and adverse events. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching and cross-switching among biosimilars.[83] There should be a robust pharmacovigilance strategy to protect patients and develop the long-term evidence base required to provide patients and clinicians with the necessary assurances on safety and effectiveness. Biosimilars are likely to be produced beyond infliximab and may help reduce cost of IBD treatment throughout the Asia-Pacific region.

Part C: How to monitor response – clinical, endoscopy, biomarkers and mucosal healing

Statement 11:

Monitoring of disease activity must be performed regularly, including clinical parameters, blood/faecal biomarkers and endoscopy. Cross sectional imaging and capsule endoscopy may be performed as appropriate.

Level of agreement: (a) 95%, (b) 5%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-2

Classification of recommendation: A

The target of IBD treatment includes the resolution of symptoms and intestinal inflammation; therefore, regular monitoring of inflammatory activity is essential for the optimization of IBD treatment.[84] Clinical response to treatment should be assessed 3-monthly[84] based on symptoms (such as abdominal pain and diarrhea in patients with CD or rectal bleeding and bowel habit in patients with UC[84,85], or by using clinical disease activity scores[84,86] such as CD Activity Index[87,88] or Harvey-Bradshaw Index[89] in CD and the partial Mayo Clinic index,[90,91] simple clinical colitis activity index in UC. The resolution of intestinal inflammation or mucosal healing should be monitored given that mucosal healing is associated with improved outcomes in the need for corticosteroids, hospitalization, sustained clinical remission, and decreased need for surgery in CD[92–94] and UC.[92,95] Clinical symptoms does not necessarily correlate with mucosal healing.[96,97] Endoscopic assessment, therefore, should be performed after starting treatment 6-9 months in CD and 3-6 months in UC.[84] C-reactive protein and fecal calprotectin are not a target in IBD treatment but may guide objective assessment of disease activity. The normalization of C-reactive protein and/or fecal calprotectin at week 10-14 of treatment is associated with improved outcomes of clinical remission and mucosal healing in CD[98–101] and UC.[100,102,103] Cross-sectional imaging,

to date, is not formally considered treatment target in UC,[84,104] but play a role in the assessment of CD lesions beyond the reach of endoscopy.[84,86]

The clinical response in CDs may not correlate with small bowel mucosal healing due the disconnect between small bowel mucosal inflammation despite clinical remission.[105–109] Improvement of inflammation in one location may not parallel improvement in other sites[110]. Therefore, the assessment of small bowel mucosal healing in areas that are beyond the reach of esophagogastroduodenoscopy and ileocolonoscopy should be considered as well. Video capsule endoscopy is effective for assessment of small bowel mucosal healing[111] and may be superior to magnetic resonance enterography in the evaluation of proximal small bowel lesions[112]. The Lewis score and Capsule Endoscopy Crohn's Disease Activity Index have been validated for the assessment of disease activity and mucosal healing using video capsule endoscopy.[113,114] However, the price of video capsule endoscopy is high, so it may be more cost-effective in high risk patients such as those who have had multiple small bowel resections or with aggressive small bowel disease[115].

Capsule retention rate was as high as 13% in patients with established CD, but only 1.6% in patients with suspected CD[116]. Capsule retention rate in the latter group without obstructive symptoms, history of small bowel resection or known stenosis had been reported to be comparable to patients with obscure GI bleeding[117–119]. Small bowel patency capsule prior to capsule endoscopy, therefore, is not considered necessary in most CD patients. There is a strong correlation in severity and extent of disease between the colon capsule endoscopy and conventional colonoscopy in patients with UC[120,121]. However, colon capsule endoscopy may underestimate both severity and extent of disease.[122,123] Colon capsule endoscopy has

several limitations including inability to obtain biopsy specimens, chance of incomplete colon capsule endoscopy examination and need for more thorough bowel cleansing preparation.[124] As a result, colon capsule endoscopy cannot substitute colonoscopy for monitoring of disease activity in patients with UC.

Part E: Withdrawing immunomodulators/ anti-TNF drugs in IBD

Statement 12:

In selected CD and UC patients on combination therapy who have absence of surgery history or fistula, normal C-reactive protein and fecal calprotectin level, anti-TNF therapy withdrawal while continuing immunomodulator can be considered if the patient is in clinical and endoscopic remission.

Level of agreement: (a) 76%, (b) 19%, (c) 0%, (d) 5%, (e) 0%.

Quality of evidence: II-1

Classification of recommendation: B

Little is known about the optimal duration of anti-TNF therapy and/ or an immunomodulator for patients with IBD but there are emerging data to guide us. Louis *et al.* (STORI) evaluated 115 CD patients in remission for at least 6 months on dual treatment with infliximab and azathioprine. Infliximab was stopped and patients were followed for 1 year whereby, 39% of patients relapsed despite continuing azathioprine. Response was regained in 88% patients when infliximab was restarted. Patients with a low risk of relapse can be identified using a combination of clinical and biologic markers including low C-reactive protein and faecal calprotectin level and absence of surgical resection.[47] In a follow-up of the STORI cohort up to 7 years, 20% of the patients who did not restart infliximab or another biologic agent and did not develop major complications and 70% of these patients

had no failure resulting from the de-escalation strategy.[125] Maintenance of immunomodulator treatment after anti-TNF discontinuation was associated with reduced risk of relapse. Patients with perianal fistulas with good response to anti-TNF therapy have a higher risk of relapse on stopping compared with luminal CD, hence anti-TNF discontinuation is not generally recommended in this population.[126]

In adult UC patients, stopping anti-TNF therapy resulted in relapse rates of 14-42% at 12 months and 25-47% at 24 months. Relapse rate were lower in studies which included mucosal healing as part of the definition of remission. In a recent meta-analysis, approximately 50% of patients who discontinued anti-TNF agents after combination therapy maintained remission 2 years later but the proportion in remission reduced over time. Importantly, resuming the same anti-TNF in patients who relapse following anti-TNF withdrawal for sustained remission is usually safe and effective. Markers of disease activity, poor prognostic factors, and complicated disease course were associated with increased relapse.[46]

Statement 13:

The decision to withdraw a drug should be made for each individual based on patient preference, disease activity markers, risk of relapse, safety, and cost.

Level of agreement: (a) 95%, (b) 5%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-1

Classification of recommendation: A

It is important to individualize therapy in patients with IBD. Although effective, anti-TNF agents are expensive and may cause severe adverse event, such as infection and malignancy.

Decision analysis models have established that anti-TNF agents are cost-effective in the short term but data are unclear for long term. In Asia, special considerations are required for stopping anti-TNF therapy due to cost, economic burden, high prevalence of infections especially TB, and availability of alternative drugs. When considering stopping drugs in IBD, markers of disease activity, prognostic factors, and past history of disease course or relapse need to be taken into consideration.[46] Subjects with complex IBD, endoscopically active disease, short disease duration, post-surgical and elevated C-reactive protein probably should not stop anti-TNF as their risk of relapse is high and consequence of chronic disease activity likely to result in intestinal damage. In contrast, patients in clinical, biochemical, and endoscopic remission are more likely to remain well when anti-TNF or immunomodulators are stopped. Reintroduction of the same treatment is usually, but not always, successful and close clinical monitoring is required upon any treatment withdrawal. The decision on treatment withdrawal is also based on patient preference. Patients with subclinical disease activity are at much higher risk of relapse when any treatment is reduced or withdrawn. Before withdrawal of any maintenance IBD therapy, re-evaluation of disease activity using a combination of clinical, biochemical, endoscopic/histological, and/or radiological techniques should be performed to assess risks and benefits of stopping.[126] In developing or newly industrialized countries which lack reimbursement of biological agents, cost may be an issue which leads to treatment withdrawal. Therefore, discontinuation of therapy needs to be personalized on a case-by-case basis.

Statement 14:

Stopping azathioprine or mercaptopurine mono-therapy in patients with CD and UC is associated with a high risk of relapse and should not be encouraged unless the patient has been in clinical remission for more than 4 years.

Level of agreement: (a) 48%, (b) 48%, (c) 4%, (d) 0%, (e) 0%.

Quality of evidence: I

Classification of recommendation: A

In CD, a multi-center double-blind study of azathioprine-treated patients, in clinical remission for over 3 years found that cumulative risk of relapse after withdrawal at 1, 3 and 5 years was 14%, 53%, and 63%, respectively.[127] Several subsequent controlled trials also showed higher relapse rates in the drug withdrawal arm, from 8% to 25% at 6 months, 17% to 53% at 12 months, 21% to 31% at 18 months, and 31% at 24 months.[126,128] In UC, there are fewer studies of stopping immunomodulator monotherapy. For UC patients in short-term remission with azathioprine, 1-year relapse rates was seen in 59% with azathioprine withdrawal.[129] Overall in both CD and UC, there is high cumulative risk of relapse overtime after withdrawal of immunomodulator monotherapy and it is estimated that approximately one third of patients relapse by 2 years and half to three quarters relapse by 5 years.[126,127,130,131]

It is therefore important to consider in conjunction with the patient, the risks and benefits of continued immunomodulator monotherapy for IBD patients treated for 3–4 years if there is no evidence of continuing disease activity.[132] Factors predictive of relapse following withdrawal of immunomodulator monotherapy include raised markers of subclinical disease activity and disease extent/localization such as peri-anal disease in CD or extensive disease

in UC.[46] Consistent factors associated with disease relapse in CD after stopping immunomodulators included high C-reactive protein, low hemoglobin levels, and increased leukocyte count whereas for UC these included increased leucocyte count, number of relapses on azathioprine and shortened duration on azathioprine. The BERENICE study modeled mortality risk in CD patients according to immunomodulator use, age, and disease extent and favored sustained immunomodulator treatment in CD patients with extensive colitis, irrespective of age.[133]

Statement 15:

In selected CD and UC patients with absence of surgery or fistula, normal C-reactive protein, normal fecal calprotectin level and endoscopic healing withdrawing of biological monotherapy can be considered if the patient is in clinical remission for more than 4 years.

Level of agreement: (a) 26%, (b) 37%, (c) 37%, (d) 0%, (e) 0%.

Quality of evidence: II-3

Classification of recommendation: B

There remains a lack of high quality studies on stopping monotherapy for anti-TNF in patients with IBD. Such patients usually require anti-TNF or biological drugs because of previous poor disease control, therefore stopping anti-TNF therapy completely might not be appropriate. More studies are needed ideally randomized controlled trials, to compare the anti-TNF discontinuation strategy with a control group where the anti-TNF is maintained, in those with different disease course or those who started therapy at different disease time point. It is possible that early treatment resulting in deep mucosal healing may allow ceasing therapy in selected subjects. Thus, this statement has been rejected.

Part F: Pharmacogenetics for TPMT and NUTD15

Statement 16:

TPMT testing prior to thiopurine commencement is of limited value in Asian populations. Hence routine measurement is not recommended.

Level of agreement: (a) 71%, (b) 29%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-3

Classification of recommendation: C

Thiopurines undergo complex metabolism that leads to the formation of the active and potentially myelotoxic metabolite, 6-thioguanine, as well as inactive and potentially hepatotoxic metabolite, 6-methyl mercaptopurine. Two genes are known to be associated with leukopenia in patients on thiopurines; TPMT and NUTD15. The gene encoding TPMT is polymorphic, leading to a large variation in enzyme activity between individuals. Both genotyping and phenotyping studies have shown ethnic variations in gene sequencing and enzyme activity worldwide, with at least 29 mutations in the TPMT gene identified to date.[134]

Low TPMT enzyme activity leads to increased conversion of thiopurines to 6-thioguanine via the hypoxanthine phosphoribosyltransferase pathway. Minimal TPMT activity can cause early, potentially life-threatening myelosuppression in the setting of thiopurine use. Epidemiological studies in the Caucasian population have shown a trimodal distribution of TPMT enzyme activity, with 89% having normal or high activity, 11% having intermediate activity and 0.3% having minimal activity.[135] The utility TPMT testing in personalizing thiopurine treatment has remained controversial in the Asian population. TPMT variants are generally rare among Asian populations.[136] Interestingly, although the frequency of

TPMT mutations is lower in the Asians compared to the Caucasians (~3% versus ~10%), the frequency at which thiopurine-induced leukopenia occurs in Asians is paradoxically considerably higher; 5% in Caucasians compared to 35.4% in Korean,[137] 15.8% in Japanese[138] and 18.1% in Chinese.[139] The thiopurine dose given in these group of patients were also much less than the recommended weight-based dosing. Hence, more frequent and severe leukopenia is expected with standard doses of thiopurines in this population. This suggests that TPMT genotyping or phenotyping does not seem to be very useful in Asian population and also highlights the existence of other underlying race specific genetic polymorphisms in thiopurine response.

Statement 17:

In the Asian population, NUDT15 genotyping, prior to thiopurine commencement is recommended if available.

Level of agreement: (a) 89%, (b) 11%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-2

Classification of recommendation: B

The NUDT15 gene codes for an enzyme in the regulation of 6-thioguanine concentrations by converting 6-thioguanosine triphosphate to 6-thioguanosine monophosphate.[140] Recent genome-wide association studies described a missense variant in the NUDT15 gene rs116855232 (c.415C>T or p.Arg139Cys variant) that is strongly associated with thiopurine-related myelosuppression in patients with IBD[4] and in children with acute lymphoblastic leukaemia (ALL).[141] NUDT15 genetic variation is substantially over-represented in Asians and is their predominant genetic cause for thiopurine toxicity.[137,141] The NUDT15 risk allele encoding p.Arg139Cys is more common in Asians than in Caucasians, with reported allele

frequencies of 10.4% in Koreans, 7% in Japanese, 13% in Chinese and 2% in an admixed American population.[137]

Yang *et al.* identified the NUDT15 variant (p.Arg139Cys) as a significant risk factor for thiopurine-induced early leukopenia in KoreanCD patients.[137] 978 CD patients were included in the study. The p.Arg139Cys risk variant was present in 89.4% (59/66) of cases developing early leukopenia but in only 6.8% (43/632) of controls. This NUDT15 allele had a sensitivity of 89.4% (59/66), specificity of 93.2% (589/632) and an area under the curve (AUC) value of 0.92 for early leukopenia. In addition, there was a positive gene dose effect of the NUDT15 risk allele in development of thiopurine associated leucopenia. As the number of copies of the NUDT15 risk allele increased, the dose of thiopurines at which leukopenia occurred decreased, the interval from the onset of thiopurine therapy to the development of leukopenia decreased and the grade of the observed leukopenia increased.

The results of this study were reproduced in a study of 663 children with acute lymphoblastic leukaemia (ALL).[141] The NUDT15 variant was absent from the African population, uncommon in Europeans and it was the most prevalent in East Asians and Hispanics. These NUDT15 variants are highly penetrant. Patients with the TT genotype at rs116855232 (homozygous for the risk allele at p.Arg139Cys) were very sensitive to mercaptopurine (MP), with an average dose intensity of 8.3%, compared with patients with TC and CC genotypes, who tolerated 63% and 83.5% of the planned dose, respectively.

Such association has been demonstrated by multiple independent studies. Recently published systemic review and meta-analysis, included 7 studies with total of 1138 patients with IBD or ALL, of which 311 patients carried the NUDT15 415T allele.[142] This meta-analysis provided evidence that T carriers of this NUDT15 c.415C>T variant were significantly correlated with high incidences of thiopurine-induced leukopenia. This correlation was especially strong in TT patients, where it was found to be significantly increased by 6.54-fold. They also found that the NUDT15 c.415C>T variant was common in Asians and Hispanics, but rare in Europeans and Africans; the frequency of the NUDT15 c.415C>T distribution varied substantially by race/ethnicity. (See Table 2)

This strongly indicates the potential of NUDT15 genotype, particularly c.415C>T (rs116855232) variant, to guide individualised thiopurine dosing to mitigate toxicity, with the same principle used for TPMT based dose adjustments, especially in the Asian population. Therefore, integration of NUDT15 analysis in thiopurine dosing algorithm may have a major implication for Asian populations, whereas TPMT variants are most informative for thiopurine toxicity in Europeans and Africans. A dosing algorithm that incorporates NUDT15 variants would potentially provide a robust approach to personalise thiopurine therapy in the Asian population.

Statement 18:

In patients with CD and UC we recommend a steady state trough infliximab level between 3 and 7µg/mL and adalimumab trough level between 4 and 8µg/mL.

Level of agreement: (a) 45%, (b) 41%, (c) 14%, (d) 0%, (e) 0%.

Quality of evidence: II-2

Classification of recommendation: B

Anti-TNF drug concentrations and of anti–drug antibodies may help to correlate with clinical outcomes. Studies have proposed several different optimal cut-off levels. This variability is explained by multiple factors:

a) The heterogeneity of the available assays. Different assays have been used and they are not necessarily equivalent making extrapolation difficult; and

b) The diversity of studies outcomes. The studies used to derive different target trough concentrations were studies of patients on maintenance therapy in various stages of response or remission.

Table 3 summarizes the potential target infliximab trough drug level from the existing literature to predict clinical disease activity. According to the studies, infliximab trough > 3 µg/mL is predictive of failure to respond to dose escalation, and also remission rates appear to plateau for infliximab trough levels above 7µg/mL. Based on the currently available evidence, we suggest target trough concentrations of 3-7 µg/mL for infliximab.

Table 4 summarizes the potential target adalimumab level from the existing literature to predict clinical disease activity. For adalimumab, a trough greater than 4 µg/mL was predictive of non-response to dose escalation, and remission rates plateau above 8 µg/mL.

The upper limit of the therapeutic range for adalimumab is less well defined compared to infliximab. Based on the currently available evidence, we suggest target trough concentrations of 4-8 µg/mL for adalimumab. For patients who are not in clinical remission and have limited therapeutic options beyond the anti-TNF agent they are on, we recommend aiming for therapeutic levels in the higher end of the quoted therapeutic range.

Statement 19:

Trough levels higher than the standard range may be appropriate for those with fistulizing CD or in aiming for mucosal healing.

Level of agreement: (a) 45%, (b) 41%, (c) 14%, (d) 0%, (e) 0%.

Quality of evidence: II-3

Classification of recommendation: C

A different target therapeutic range for infliximab or adalimumab may be appropriate for specific treatment end-points and/or disease phenotypes. Higher trough levels are often needed to achieve endoscopic remission or mucosal healing and closure of fistulas in CD. In a retrospective cross-sectional study of 145 IBD patients treated with infliximab or adalimumab, for endoscopic remission, an optimal infliximab trough level appears to be 6 to 10µg/mL, while an optimal adalimumab trough appears to be 8 to 12 µg/mL.[156]

Studies have shown that a higher infliximab trough level is required to heal perianal fistulizing CD. A retrospective cross-sectional study looking at 117 CD patients with perianal fistula treated with infliximab for at least 24 weeks, assessed the correlation between perianal fistula healing and trough levels of infliximab.[31] There was a linear relationship between quartiles and fistula healing when infliximab levels were stratified by quartiles.

Infliximab trough level cut-offs above 2.9µg/mL, 10.1µg/mL and 20.2µg/mL were associated with fistula healing rates of 65%, 79% and 86%, respectively. In the multivariate analysis, only infliximab level ≥10.1 µg/mL maintained statistical significance for fistula healing. Data on adalimumab levels for healing in fistulizing CD is lacking. Based on the same study, in the context of mucosal healing, when infliximab levels were stratified by quartiles, there was again a linear relationship between quartiles and mucosal healing.[31] infliximab trough level cut-offs above 2.9µg/mL, 10.1µg/mL and 20.2µg/mL were associated with mucosal healing rates of 65%, 79% and 86%, respectively. In the multivariate analysis, infliximab level < 10µg/mL was independently associated with lack of mucosal healing. These studies suggest that higher infliximab levels are associated with fistula and mucosal healing. Drug levels higher than what has been described for clinical remission may be needed to achieve mucosal healing and fistula resolution in CD. In a retrospective cross-sectional study of 145 IBD patients treated with infliximab or adalimumab, for endoscopic remission, an optimal infliximab trough level appears to be 6 to 10µg/mL, while an optimal adalimumab trough appears to be 8 to 12 µg/mL.[156] Studies have shown that a higher infliximab trough level is required to heal perianal fistulizing CD. A retrospective cross-sectional study looking at 117 CD patients with perianal fistula treated with infliximab for at least 24 weeks, assessed the correlation between perianal fistula healing and trough levels of infliximab.[31] When infliximab levels were stratified by quartiles, there was a linear relationship between quartiles and fistula healing. Infliximab trough level cut-offs above 2.9µg/mL, 10.1µg/mL and 20.2µg/mL were associated with fistula healing rates of 65%, 79% and 86%, respectively. In the multivariate analysis, only infliximab level ≥10.1 µg/mL maintained statistical significance for fistula healing. There are few data on adalimumab levels for healing in fistulizing CD.

Based on the same study, in the context of mucosal healing, when infliximab levels were stratified by quartiles, there was again a linear relationship between quartiles and mucosal healing.[31] Infliximab trough level cut-offs above 2.9µg/mL, 10.1µg/mL and 20.2µg/mL were associated with mucosal healing rates of 65%, 79% and 86%, respectively. In the multivariate analysis, infliximab level < 10µg/mL was independently associated with lack of mucosal healing. These suggest that infliximab levels are associated fistula and mucosal healing. Drug levels higher than what has been described for clinical remission may be needed in order to achieve therapeutic success in mucosal healing and penetrating CD, even more so in penetrating CD.

These consensus statements favored use of reactive therapeutic drug monitoring (TDM) in patients with active IBD to help guide management. An algorithm of TDM of biological agent testing in IBD is summarized in Figure 1. The testing of anti-drug antibodies is variable between different commercial assays and there is no standardized reporting of these values. There is, therefore, greater variability in the detection of anti-drug antibodies than anti-TNF drug levels between different assays. Low-titre anti-drug antibodies may be transient and non-neutralising. In contrast, high-titre antibodies, especially with undetectable trough drug concentrations, are generally persistent and neutralising and associated with loss of treatment efficacy. No anti-drug antibody cut-offs have been established to date to differentiate high from low antibody titres. An ideal assay is one that has cut-offs that directly correlate against clinical data.

Statement 20:

Patients with active inflammatory disease and therapeutic drug trough levels (suggesting pharmacodynamic failure) should ideally be switched out of class but switch within class may be effective.

Level of agreement: (a) 33%, (b) 48%, (c) 19%, (d) 0%, (e) 0%.

Quality of evidence: II-3

Classification of recommendation: C

If drug trough levels were within the therapeutic range, active inflammatory disease needs to be objectively confirmed with endoscopy, histology, imaging and/or fecal calprotectin. Confirmation of active inflammation is indicative of pharmacodynamic failure, suggestive that non-TNF driven inflammatory pathways may predominate and there may not be significant benefit from anti-TNF dose escalation or switching to another anti-TNF agent. Subjects should instead be ideally switched out of class. In a retrospective study of 247 Israeli IBD patients with loss of response to either infliximab or adalimumab, the correlation between the outcomes of different interventions and trough levels of drug or anti-drug antibodies during loss of response was evaluated.[157] In cases with adequate infliximab or adalimumab drug trough levels at the time of loss of response, the clinical efficacy was significantly better after switching out of class than for anti-TNF dose increase or switching to another anti-TNF drug. A small proportion of patients did recapture response by switching within class. In countries with limited availability of biological agents available, switching within class may be attempted. Alternatively, referral to a specialised IBD centre that is recruiting subjects for clinical drug trials can also be recommended.

Statement 21:

Patients with active inflammatory disease and undetectable drug trough levels and no anti-drug antibodies (suggesting non-immune mediated pharmacokinetic failure) should have adherence checked first followed by anti-TNF dose escalation.

Level of agreement: (a) 70%, (b) 30%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-3

Classification of recommendation: C

In this scenario once non-compliance is excluded, the patient may have non-immune mediated pharmacokinetic failure. Non-immune mediated pharmacokinetic failure is due to under-dosing or the anti-TNF agent being rapidly cleared via a mechanism other than anti-drug antibodies. Non-immune mediated pharmacokinetic failure responds better to dose escalation rather than switching within class. Following dose escalation, we recommend repeating therapeutic drug monitoring once steady state is again achieved.

Subtherapeutic drug levels & negative anti-drug antibodies may also occur early in immune mediated pharmacokinetic failure (if low anti-drug antibodies titers complex with anti-TNF drugs and are cleared from the circulation). Repeat testing following dose escalation may detect those with early immune-mediated pharmacokinetic failure, as on repeat testing drug levels may become undetectable with detectable anti-drug antibodies.

Statement 22:

Patients with active inflammatory disease and undetectable drug trough levels & low titres of anti-drug antibodies, which suggests immune mediated pharmacokinetic failure, should have an immunomodulator added or optimised and/or anti-TNF dose escalation.

Level of agreement: (a) 64%, (b) 36%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-3

Classification of recommendation: B

Low titers of anti-drug antibodies may be overcome with the addition of- or optimization of an immunomodulator and/or anti-TNF dose escalation. If the patient is not significantly unwell, a stepwise approach may be taken by adding or optimizing an immunomodulator followed by dose escalation if the former fails to achieve remission. If on repeat testing, drug levels are still undetectable with positive anti-drug antibodies, regardless of titers, the patient should be treated as per Statement 23.

Statement 23:

Patients with active inflammatory disease and undetectable drug trough levels & high titres of anti-drug antibodies suggest immune-mediated pharmacokinetic failure. Options include addition or optimisation of an immunomodulator, and/ or switching within or out of class.

Level of agreement: (a) 68%, (b) 32%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-2

Classification of recommendation: B

To understand the rationale behind the recommendations, these are the evidence looking at a) The outcome of dose intensification or switch according to anti-drug antibodies titers; and b) The role of immunomodulators on anti-TNF drug level and immunogenicity.

In a retrospective study of 247 IBD patients with loss of response to infliximab or adalimumab, the effect of dose intensification in patients with high-titer anti-drug antibody and no/low-titer anti-drug antibody was studied.[157] There was no difference in the anti-TNF drug level after dose intensification in patients with high-titer anti-drug antibodies. In contrast, dose intensification significantly increased anti-TNF drug levels in patients with no/low anti-drug antibodies titers. Van de Casteele et al. evaluated 90 IBD subjects with loss of response to infliximab[158] and found in those with low levels of antibodies against infliximab (< 9.1 U/ml), infliximab dose intensification was able to recapture response. In contrast, patients with sustained levels of antibodies against infliximab of >9.1 u/ml had a poorer response to dose intensification.

A prospective study on 82 IBD patients[155] examined the impact of TDM on loss of response to adalimumab. They found that in those with low anti-drug antibody titres against adalimumab, dose intensification was able to recapture response compared to patients with high anti-drug antibodies. However, in the group with high level of anti-drug antibodies to adalimumab, upon switching to infliximab, they were able to recapture response in a significant proportion of patients. Based on a retrospective study of 247 IBD patients,[157] in those with loss of response with no/low antidrug antibody levels to either adalimumab or infliximab, dose intensification resulted in a significantly longer duration of recapturing response than switching to another anti-TNF. However, in cases with loss of response with

high antidrug antibody levels to either adalimumab or infliximab, switching to another anti-TNF resulted in a significantly longer duration of regained response than dose intensification.

With the conventional thiopurines weight-based dosing regimen (2.0–2.5 mg/kg/day azathioprine and 1.0–1.5 mg/kg/day 6-mercaptopurine), placebo-controlled studies reported response rates between 42% and 80%.[159–161] Given the variable results using conventional dosing, thiopurine metabolite measurements are increasingly being used to optimise thiopurine therapy in IBD and improve clinical outcomes.

Data suggest that 6-thioguanine nucleotide concentrations in excess of 235 pmol/8 $x10^8$ erythrocytes are associated with clinical remission in a significant proportion of patients.[162,163] The 6-thioguanine nucleotide upper limit is based on studies showing that the proportion of patients in remission does not increase significantly with 6-thioguanine nucleotide concentrations greater than 450 pmol/8 $x10^8$ erythrocytes, whereas there is an increased risk of myelotoxicity above this level.[162,164,165] The dose of thiopurine correlated poorly with 6-thioguanine nucleotide levels ($r = 0.0009$).[162]

Dose optimisation studies using 6-thioguanine nucleotide levels have also been reported. Two retrospective Australian studies have shown that optimisation of thiopurines in patients with sub-therapeutic 6-thioguanine nucleotide levels can lead to improvement in clinical outcomes in 88% and 78% of patients after dose escalation of thiopurines, respectively.[166,167] A pivotal metabolite study demonstrated that high levels of 6-methylmercaptopurine were associated with hepatotoxicity with elevated levels of transaminases. The incidence of hepatotoxicity in this study was 17% with median 6-

methylmercaptopurine levels of 5463 pmol/8 x10^8 erythrocytes in those patients with abnormal liver function tests compared to 2213 pmol/8 x10^8 erythrocytes in those with normal liver function tests ($p < 0.05$). The risk of hepatotoxicity increased threefold (18 vs 6%, $p < 0.05$) when 6-methylmercaptopurine exceeded 5700 pmol/8 x10^8 erythrocytes.[4] There was no correlation of 6-methylmercaptopurine levels with clinical efficacy or thiopurine dose. Hence, the therapeutic range for use in clinical practice for 6-thioguanine nucleotide is 235–450 pmol/8 x10^8 erythrocytes. For 6-methylmercaptopurine, a level of less than 5700 pmol/8 x10^8 erythrocytes mitigates the risk of hepatotoxicity.

Several studies have shown the benefit of using combination therapy with anti-TNFs and immunomodulators. The mechanism to explain the improved efficacy with combination therapy includes higher anti-TNF levels and decreased immunogenicity. There is a significant correlation between anti-TNF drug level and anti-drug antibody level, and the use of immunomodulators.[168] The SONIC study demonstrated concomitant azathioprine usage resulted in higher infliximab trough levels most likely through reduced immunogenicity.[34] Similarly, in the COMMIT trial, concomitant methotrexate was associated with a higher infliximab trough level and reduced immunogenicity.[40]

Based on a cross-sectional study, higher 6-thioguanine nucleotide levels correlate with higher trough infliximab concentrations in IBD patients on combination therapy. Patients with detectable infliximab antibodies had significantly lower 6-thioguanine nucleotide levels.[169]

Ben Horin *et al.* also showed the benefit of adding immunomodulators to revert immunogenicity and increasing infliximab levels in patients who developed anti-drug

antibodies to infliximab with subtherapeutic infliximab drug level.[38] Figure 2 summarizes the recommendation on the interpretation of TDM for anti-TNF to guide management in patients with loss of response.

Statement 24:

Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), and Hepatitis B core antibody (HBcAb) should be tested routinely before initiation of systemic corticosteroids, immunomodulators and biological agents.

Level of agreement: (a)100%, (b) 0%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-3

Classification of recommendation: B

In Asia, Hepatitis B virus (HBV) infection is endemic, and East Asia, where over 8% of males over the age of 35 are positive for the hepatitis B surface antigen, has the highest prevalence of all Asian regions[170] To minimize the risk of reactivation of the virus, immunosuppressive therapy should proceed only after screening in order to avoid life threatening situations. [171,172] HBV vaccination is recommended in patients who are negative for HBsAg, HBsAb, and HBcAb.

Statement 25:

In patients who are HBsAg and/or HBcAb positive, HBV DNA quantification is recommended before the initiation of systemic corticosteroids, immunomodulators and biological agents.

Level of agreement: (a) 77%, (b) 23%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-3

Classification of recommendation: C

In patients with IBD, 25% to 36% of those who are HBsAg positive experienced liver dysfunction.[173,174] Most cases of HBV reactivation have been observed in HBV-infected IBD patients treated with 2 or more immunomodulators for a long period of time, were positive for HBV DNA, and/or had not received prophylactic antiviral treatment.[172] Therefore, we recommend checking the HBV DNA titer before initiating systemic corticosteroids, immunomodulators and biological agents.

Statement 26:

Antiviral treatment for prophylaxis of HBV reactivation is recommended in patients with detectable HBV DNA, before initiation of systemic corticosteroids, immunomodulators and biologics.

Level of agreement: (a) 82%, (b) 14%, (c) 4%, (d) 0%, (e) 0%.

Quality of evidence: II-2

Classification of recommendation: A

Patients with no antiviral therapy should be monitored closely and antiviral treatment initiated when there is increase in HBV DNA titre. It is recommended for patients with detectable HBV DNA to undergo antiviral prophylaxis using nucleotide/nucleoside analogues.

The treatment should start 2 weeks before the commencement of immunomodulators. Prophylaxis should continue for 6-12 months after discontinuation of immunomodulators. Entecavir and tenefovir have a rapid onset of action, high antiviral potency, and low incidence of resistance, and are preferred in patients with IBD.[172]

Statement 27:

Routine screening for latent TB infection should be performed according to local practice before initiating biologic treatment. This may include chest X-ray, chest CT, interferon-gamma release assays (IGRA) and/or tuberculin skin test (TST).

Level of agreement: (a) 77%, (b) 18%, (c) 5%, (d) 0%, (e) 0%.

Quality of evidence: II-2

Classification of recommendation: A

Due to the use of immunosuppressive therapy, patients with IBD are at higher risk of active TB infection than the general population.[172] Extra-pulmonary TB is more common in patients on immunosuppressive agents, compared to the general population (30% vs 13%, in Taiwan, respectively).[175–177] Atypical presentation and disseminated disease is also more common in patients treated with anti-TNF, making diagnosis more difficult.[172] In Taiwan, 5.8% of cases of extra-pulmonary TB were reported to have occurred in the gastrointestinal tract.[178] Screening for latent TB should be performed in all CD patients prior to biologic therapy through physical examination, chest radiography, and TST or IGRA (QuantiFERON-TB GOLD). It should be noted that results of TST is affected by prior Bacille Calmette-Guerin(BCG) vaccination, whereas IGRA is unaffected by prior BCG exposure.[179]

Statement 28:

In patients diagnosed with latent TB, prophylactic treatment for the prevention of TB reactivation is effective, therefore, chemoprophylaxis should be started (preferably 3-4 weeks) before the use of biological agents.

Level of agreement: (a) 77%, (b) 23%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: II-3

Classification of recommendation: A

Chemoprophylaxis is highly effectively in decreasing the risk of TB reactivation in patients with latent TB receiving the anti-TNF treatment.[180] Treatment of latent TB should follow the current local guideline recommendations.[172,178] Although there is no robust data, ECCO[181] as well as AOCC/APAGE[182] guidelines and most authorities suggest that it should be safe to start the biologic agents at least 3 to 4 weeks) after the initiation of anti-TB drugs according to the clinical experience and observational study.[183,184] Consultation with an infectious disease or chest specialist for multidisciplinary care is recommended. [172,178]

Statement 29:

During biological therapy, patients should be monitored for contact history, symptoms and signs of active TB. Regular chest X-ray and IGRA may be considered.

Level of agreement: (a) 68%, (b) 32%, (c) 0%, (d) 0%, (e) 0%.

Quality of evidence: III

Classification of recommendation: B

Patients with IBD receiving biologic treatment should be monitored regularly for signs and symptoms of active TB disease. Chest radiography and IGRA should be performed ideally every 6 months, or at least annually in clinical practice for IGRA.[178] Travel and TB contact

history should be monitored while the patient is receiving immunosuppressive treatment. An infectious disease specialist should be consulted when necessary.

Conclusions

The use of immunomodulators and biological agents for the management of IBD is increasingly common. The data demonstrating the safety, efficacy of biological agents such as infliximab, adalimumab and their corresponding biosimilars has been reviewed and discussed in this paper. We have also described strategies for initiation and de-escalation when considering the administration of these drugs in Asia. Special consideration must be paid to the risk of under-treatment due to financial constraints leading to episodic treatment resulting in sub-optimal disease control. We have also highlighted HBV and TB infections, which may complicate the use of biological agents and immunomodulators. In administering immunomodulators, the data suggest that clinicians take into account the pharmacogenetics of NUTD15 in the Asian population whereas the pharmacogenetics of TMPT are not as relevant.

The use of immunomodulators and biological agents for the management of IBD is increasingly common in Asia. The data demonstrating the safety and efficacy of biological agents and their corresponding biosimilars has been summarised in these consensus statements. We have also described strategies for the initiation and de-escalation of these drugs. In Asia, under-treatment of IBD is possible due to financial constraints resulting in episodic treatment with the risk of sub-optimal disease control. We also highlighted HBV and TB infections that may complicate the use of biological agents and immunomodulators. In administering immunomodulators, the data suggest that clinicians take into account the

pharmacogenetics of NUDT15 in the Asian population whereas the pharmacogenetics of TMPT are not as relevant.

The Asia Pacific Association of Gastroenterology (APAGE) Working Group on IBD in collaboration with AOCC has endeavoured to present through this review, a comprehensive and authoritative understanding of the best practices for treating UC and CD with immunomodulators and biological agents. The consensus statements have been developed through a rigorous process according to the modified Delphi system and has been formulated with input from various experts in the region that comprise the APAGE and AOCC. These consensus statements should be read with previous consensus statements on the definition and management of IBD in previous reviews. It is hoped that these recommendations may not only guide clinicians in the best-use of biological agents and immunomodulators but also be used for hospital and national regulatory authorities to accept these drugs onto the pharmacy formulary or for reimbursement.

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Table 1: Quality of evidence, classification of recommendation, and voting on recommendations

Category and grade	Description
Quality of evidence	
I	Evidence obtained from at least 1 randomized controlled trial
II-1	Evidence obtained from well-designed control trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control study
II-3	Evidence obtained from comparison between time or places with or without interruption
III	Opinion of respected authorities, based on clinical experience and expert committees
Classification of recommendation	
A	There is good evidence to support the statement
B	There is fair evidence to support the statement
C	There is poor evidence to support the statement but recommendation made on other ground
D	There is fair evidence to refute the statement
E	There is good evidence to refute the statement
Voting on recommendation	
a	Accept completely
b	Accept with some recommendation
c	Accept with major reservation
d	Reject with reservation
e	Reject completely

Table 2: The genotype and allele frequencies of NUDT15 c.415C>T in different ethnicity[133]

		Ethnicity			
		Asians	Hispanics	Europeans	Africans
Genotype NTUD15 c.415C>T	CC	75.84%	92.34%	99.51%	100%
	CT	21.76%	7.21%	0.49%	0%
	TT	2.39%	0.45%	0%	0%
Allele	C	86.72%	95.95%	99.76%	100%
	T	13.28%	4.05%	0.24%	0%

Table 3: Target infliximab trough drug level from various studies. Obs, Observational; RCT, Randomized Controlled Trial; RIA, Radioimmunoassay; ELISA, Enzyme-linked immunosorbent assay; HMSA, Homogeneous mobility shift assay

Author	Year	Disease	Design	Number of subjects	Assay	Threshold, µg/mL
Steenholdt *et al.*[143]	2011	IBD	Obs	106	RIA	≥2.8
Bortlik *et al.*[144]	2012	CD	Obs	84	ELISA	≥3.0
Cornillie *et al.*[145]	2014	CD	RCT	144	ELISA	≥3.5
Adedokun *et al.*[146]	2014	UC	RCT	728	ELISA	≥3.7
Levesque *et al.*[147]	2014	CD	Obs	327	HMSA	≥3.0
Vande Casteele *et al.*[148]	2014	CD	Obs	483	HMSA	≥2.8
Reinisch *et al.* [149]	2015	CD	RCT	203	ELISA	≥3.0
Vande Casteele *et al.* [150]	2015	IBD	RCT	263	ELISA	≥3.7

Table 4: Target adalimumab trough drug level from various studies. ELISA, Enzyme-linked immunosorbent assay; HMSA, Homogeneous mobility shift assay

Author	Year	Disease	Design	N	Assay	Threshold
Karmiris *et al.*[151]	2009	CD	Prospective	168	ELISA	6.2-8.9
Roblin *et al.*[152]	2014	IBD	Cross sectional	40	ELISA	>4.9
Mazor *et al.* [153]	2014	CD	Cross sectional	71	ELISA	5.85
Roblin *et al.*[154]	2014	IBD	Prospective	82	ELISA	4.9
Morita *et al.*[155]	2016	CD	Retrospective	42	ELISA	5.57-7.9

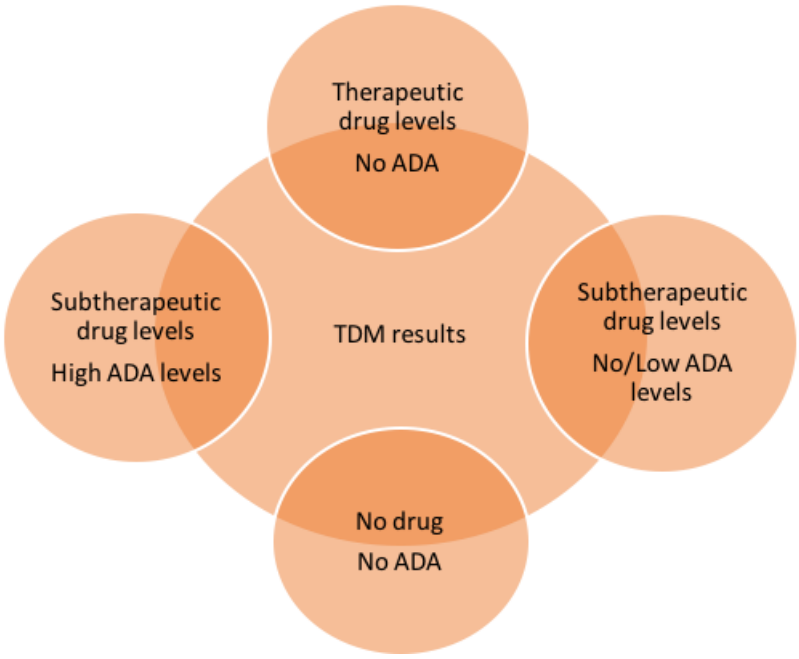

Figure 1: Possible permutation of therapeutic drug monitoring (TDM) results. TDM, Therapeutic drug monitoring; ADA, Antidrug antibody

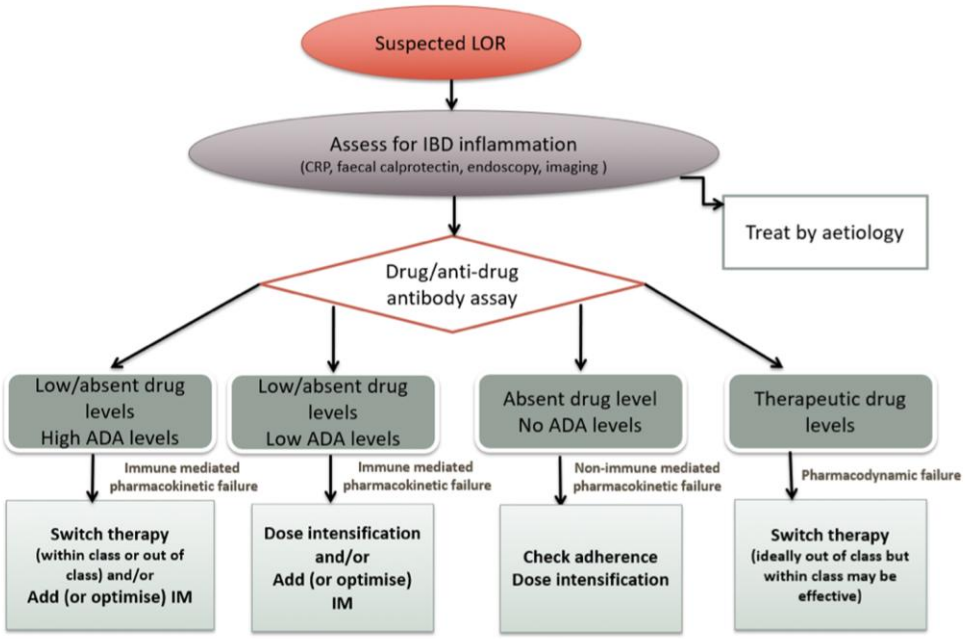

Figure 2: Summary algorithm to guide management according to therapeutic drug monitoring loss of response. LOR, Loss of response; ADA, Antidrug antibody; IM, Immunomodulator