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REVIEW ARTICLE

Asia–Pacific consensus statements on Crohn's disease. Part 2: Management

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Abstract

The Asia Pacific Working Group on Inflammatory Bowel Disease was established in Cebu, Philippines, at the Asia Pacific Digestive Week conference in 2006 under the auspices of the Asian Pacific Association of Gastroenterology (APAGE) with the goal of developing best management practices, coordinating research and raising awareness of IBD in the region. The consensus group previously published recommendations for the diagnosis and management of ulcerative colitis (UC) with specific relevance to the Asia-Pacific region. The present consensus statements were developed following a similar process to address the epidemiology, diagnosis and management of Crohn's disease (CD). The goals of these statements are to pool the pertinent literature specifically highlighting relevant data and conditions in the Asia-Pacific region relating to the economy, health systems, background infectious diseases, differential diagnoses and treatment availability. It does not intend to be all-comprehensive and future revisions are likely to be required in this ever-changing field.

Introduction

Part 2 of the Asia Pacific Consensus Statements on Crohn's disease focuses on medical and surgical treatment of Crohn's disease (CD). As with Part 1, the statements highlight treatment issues pertinent to the Asia–Pacific region including provision of local data when possible. The high background prevalence of infectious pathogens in the region, such as tuberculosis (TB), requires greater care in the use of immunosuppressive therapies especially antitumor necrosis factor (TNF) alpha biological agents. The surgical perspectives in the management of CD are covered, including perianal fistulas. The consensus statements were developed to be in general representative of the region but adaptable to individual countries.

Results

Part C: medical management

C1. Conventional management

Statement 25

The goals of treatment include induction and maintenance of remission, prevention of strictures, fistula and other complications and improving quality of life. Normalisation of inflammatory biomarkers including C-reactive protein and faecal calprotectin are other objective endpoints of therapeutic efficacy.

Level of agreement: a—89%, b—11%, c—0%, d—0%, e—0%
Quality of evidence: III
Classification of recommendation: C

CD is an incurable and progressive disease. Objectives of treatment, therefore, are induction and maintenance of remission, and minimization of complications such as stricture, fistula, dysplasia, osteoporosis, short- and long-term drug-induced toxicity, impaired quality of life, hospitalization, and surgery. Although the majority of patients have uncomplicated, nonstricturing, nonpenetrating disease at diagnosis, many eventually develop complications.[1–3] Because of the progressive nature of the disease, patients with CD are likely to require hospitalization at some point.[4] Patients with CD also have a high likelihood of surgery.[5–7]

Approximately 20% of patients with CD develop symptoms during childhood, and 5% are diagnosed before 10 years of age.[8] Additional complications of CD in the pediatric population include growth failure, pubertal delay, and osteopenia. Active or relapsing disease may slow or even arrest the progression of puberty once it has begun. Thus, inducing disease remission before the onset of puberty and maintenance of remission during the pubertal years is crucial.[9]

The targets of therapy are evolving. Control of symptoms is important to the patient, but clinical remission is no longer sufficient. Mucosal healing is emerging as a major therapeutic goal,[10,11] as it is associated with a reduced need for surgery and hospitalization,[12] and decreased development of strictures and fistulae.[13] Although long-term studies on the natural history of CD are available in the prebiological agent era,[14] short-term data are now emerging on the alteration of the natural history of CD in the era of biological agents. Biomarkers that indicate a high chance that mucosal healing has been achieved include C-reactive protein (CRP) and fecal calprotectin. Persistently high CRP levels at 5 years is associated with the need for surgery (odds ratio [OR]: 4.8, 95% confidence interval [CI] 1.5–15.1).[15] Fecal calprotectin, a neutrophil-associated protein, is a marker of intestinal inflammation that can be quantified. Its normalization may be a surrogate for controlled intestinal inflammation. Fecal calprotectin correlates better with the extent of colonic than of small bowel disease.[16]

Statement 26

Treatment of CD depends upon the extent, behaviour and activity of the disease.

Level of agreement: a—63%, b—37%, c—0%, d—0%, e—0%
Quality of evidence: III
Classification of recommendation: C

The treatment of CD depends upon the activity, location, extent, and behavior (inflammatory, stricturing, fistulizing) of the disease. Negative prognostic predictors such as young age at onset, presence of extensive disease, stricturing disease, and positive smoking history are indications for earlier institution or escalation toward higher efficacy therapies.

The severity of the disease is generally assessed using clinical indices, systemic manifestations, and the global impact of the disease on the individual's quality of life. The Harvey Bradshaw Index and Crohn's Disease Activity Index (CDAI) are commonly used in clinical drug trials.[17,18] Endoscopic severity can be assessed using the Crohn's Disease Simple Endoscopic Scoring System or the Crohn's Disease Endoscopic Index of Severity. The Rutgeert's score of endoscopic recurrence is a simple method of documenting disease recurrence at the site of intestinal anastomosis for patients who have undergone resection. The small bowel can be evaluated by computed tomography (CT)/magnetic resonance (MR) enteroclysis, or capsule endoscopy/ double balloon enteroscopy depending upon expertise, availability of tests, and risk of capsule retention caused by small intestinal stricture. Upper gastrointestinal endoscopy should also be performed at baseline, especially in pediatric patients.[19]

Statement 27

Mild to moderately active CD involving the terminal ileum or localised ileo-caecal disease should be treated with budesonide. Conventional steroids should be used if budesonide is unavailable or the patient fails to respond [I, A]. For severe disease, conventional oral or intravenous corticosteroid is the initial treatment of choice [I, A]. Surgical resection [III, C] and anti-TNF therapies are alternatives [III, C].

Level of agreement: a—42%, b—53%, c—5%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above STOP

Approximately 20% of patients with CD have disease localized to the terminal ileum or the ileo-cecal area. Mesalazine (5-amino-salicylic acid, 5-ASA) has limited efficacy in CD.[20] Oral corticosteroids are the first line of management in patients with active CD.[21,22] Conventional corticosteroids (prednisolone) are more effective than placebo at inducing remission (relative risk [RR] 1.99; 95%CI 1.51–2.64; $P < 0.00001$).[22] Enteric-coated budesonide, which has a high first-pass metabolism, has remission induction rates of 51–69% over a period of 8–12 weeks,[23] and is effective in inducing short-term remission within 8 weeks in mild to moderately active CD compared with placebo (RR:1.96, 95%CI 1.19–3.23) and mesalazine (RR: 1.63; 95%CI 1.23–2.16).[24] Budesonide induces fewer side effects than conventional steroids (RR: 0.64, 95%CI 0.54–0.76). The recommended dose of budesonide is 9 mg once daily, usually for 6 weeks, and then the daily dose tapered by 3 mg every 2–4 weeks. When disease activity is severe (CDAI > 300), conventional steroids are more efficacious than budesonide. In two studies, the pooled RR of remission was 0.52 (95% CI 0.28–0.95) in favor of conventional steroids.[25,26]

Statement 28

Sulfasalazine can be used for mild CD limited to the colon [I, A]. There is no evidence of efficacy of mesalazine [I,A]. Moderately severe or severe colonic disease should be treated with conventional corticosteroids [1,A].

Level of agreement: a—50%, b—39%, c—11%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

Sulfasalazine at 3–6 g/day has modest efficacy when compared with placebo (pooled RR 1.38[20]) and this benefit was limited to colonic CD location. Despite promising results in earlier clinical trials,[27,28] slow-release mesalazine in a meta-analysis of three placebo-controlled trials including 615 patients with active CD for 16 weeks showed a mean reduction in the CDAI of only 63 points, compared with 45 points in the placebo arm ($P = 0.04$).[20] Because this increment is not considered clinically relevant, mesalazine is not considered effective in inducing remission. In moderate to severe colonic CD, conventional corticosteroids are recommended to induce remission.[22] The formulation of extended-release budesonide using the Multi-Matrix System (MMX) system (Cortiment ®, Ferring Pharmaceuticals, Saint Prex, Switzerland) that targets colonic release is currently unavailable in Asia.

Statement 29

For extensive small intestinal disease, patients should be treated with conventional corticosteroids [III, C]. Alternatives include anti-TNF therapies and surgery [III, C].

Level of agreement: a—44%, b—50%, c—6%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

No clinical drug trials have focused on the treatment of isolated small intestinal CD. The drug of choice for inducing remission is a conventional corticosteroid.[22] For patients with mild to moderate disease activity, oral prednisolone/methylprednisolone is recommended. Patients with severe disease activity may require intravenous corticosteroids.[22] Early introduction of an anti-TNF drug should also be considered in patients with extensive small intestinal disease,[29] in order to reduce the risk of stricture, fistula formation, and the need for initial or recurrent intestinal resection. Stricturoplasty is preferable to resection, if amenable, in order to retain small intestinal length.[30,31]

Thiopurines may be used to induce remission in CD.[32,33] A Cochrane review of azathioprine (AZA) and 6-mercaptopurine (6-MP) efficacy in inducing remission for active CD demonstrated that thiopurine therapy was superior to placebo, with an OR of 2.43 (95%CI 1.62–3.64).[33] Their slow onset of action may, however, preclude them from use as the sole induction agent.

Statement 30

Patients with ileo-colonic disease should be treated with conventional corticosteroids [I, A]. Alternatives include anti-TNF therapies and surgery [III, C].

Level of agreement: a—67%, b—33%, c—0%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

The involvement of both the small and large intestine is common in patients with CD. In this situation, neither sulfasalazine nor mesalazine is an effective therapy. Corticosteroids are the mainstay for inducing remission in ileo-colonic CD.[22,23] Anti-TNF therapy may be a viable alternative.[29]

Statement 31

Active CD with a concomitant abdominal abscess should be treated with antibiotics, percutaneous or surgical drainage, followed by delayed resection if necessary, in addition to specific medical management of CD.

Level of agreement: a—42%, b—47%, c—11%, d—0%, e—0%
Quality of evidence: III
Classification of recommendation: C

The clinical course of CD can be complicated by abdominal abscesses. Abdominal abscesses should be excluded especially in the presence of fever, abdominal pain, and abdominal tenderness. Clinical examination for a phlegmon, abdominal CT scan, or ultrasound can aid in the diagnosis and localization of abscesses. Based on small case series and expert opinion, an abscess can be treated with percutaneous drainage, antibiotics, and optimization of the medical treatment for control of disease activity, if there is no evidence of intestinal obstruction. In the presence of intestinal obstruction, an abscess should be drained and disease activity controlled before definitive intestinal surgery.[34,35]

Statement 32

Oesophageal or gastro-duodenal CD is treated with conventional corticosteroids and thiopurines or methotrexate. Use of a proton pump inhibitor should be considered for upper gastrointestinal symptoms.

Level of agreement: a—38%, b—44%, c—18%, d—0%, e—0%
Quality of evidence: III
Classification of recommendation: C

Gastroduodenal involvement usually occurs with concomitant distal small bowel or colonic disease, which determines the mode of treatment in most cases, except in the case of obstructive gastroduodenal symptoms.[36–38] Isolated esophageal or gastroduodenal CD is uncommon,[36] and there is no evidence from high-quality studies to guide the management of such patients. Standard approaches with corticosteroids and immune-modulating agents are generally applied. Because it is presumed that gastric acid may perpetuate gastroduodenal ulcers and symptoms, acid suppression combined with immunosuppressive therapy is commonly prescribed.[39]

Statement 33

Treatment for the maintenance of remission should be recommended in almost all CD patients. [II-2, B]. Conventional corticosteroid and budesonide are not recommended in the maintenance of remission [I, A]. The first line of treatment for maintenance of remission is thiopurines. Methotrexate can also be used [I, A].

Level of agreement: a—47%, b—47%, c—6%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

In clinical trials for the maintenance of remission, relapse rates among patients receiving placebo range from 30% to 60% at 1 year, and from 40% to 70% at 2 years.[40,41] Therapeutic options for the maintenance of remission depend upon the course of the disease, the extent of disease, and the effectiveness and tolerability of treatments previously used for inducing remission or maintenance. Medication adherence needs to be considered with attention toward both unintentional nonadherence (forgetting doses, prescription affordability) and intentional nonadherence (not accepting necessity of medications or fear of side effects).[42,43] Neither conventional corticosteroid nor budesonide therapy is effective in maintaining sustainable remission.[44] 5-ASA preparations are not superior to placebo for the maintenance of remission in CD.[45–47]

First line of maintenance therapy is thiopurines or methotrexate.[32,44] In a Cochrane systematic review including eight RCTs, the overall remission rate was 71% (95%CI 64–77%) for AZA and 51% (95%CI 36% to −66%) for 6-MP. AZA at a dose of 2–2.5 mg/kg is superior to 1 mg/kg.[42] The dose of thiopurine should be optimized for the individual, according to toxicity and tolerability, and be different between individuals. Parenteral methotrexate induces remission (25 mg/week), maintains response (15 mg/week), and is superior to placebo.[48] Subcutaneous administration of methotrexate appears to be a satisfactory and practical method for parenteral dose delivery.[49] Anti-TNF therapy is also an effective maintenance therapy. Ileal resection is an alternative for those with localized disease.

Statement 34

Patients on thiopurines need close monitoring for myelotoxicity and hepatotoxicity. More evidence of the benefit of thiopurine methyl transferase (TPMT) testing in Asia is required before its routine use can be recommended.

Level of agreement: a—74%, b—26%, c—0%, d—0%, e—0%
Quality of evidence: III
Classification of recommendation: C

Up to 20% of patients on AZA develop adverse events. The most common are allergic reactions (fever, arthralgia, and rash) that characteristically occur within 2–3 weeks and cease rapidly when the drug is withdrawn.[50–52] More serious side effects include bone marrow suppression and hepatotoxicity, which occur frequently in patients with a thiopurine methyl transferase (TPMT) mutation.[51] Leucopenia and hepatotoxicity can occur early or at any time during therapy. Both are reversible by cessation or reducing the dosage of the drug. Because both are asymptomatic in the earlier stages, but can lead to serious complications (e.g. severe infection), it is imperative that hematological and liver function indices are regularly monitored during thiopurine therapy. The risk of myelosuppression during thiopurine therapy is greatest within the first 8 weeks of treatment.[52,53] It is generally recommended that full blood count and liver function tests be checked within 2 weeks of initiating or increasing the dosage, then after 2, and 4 weeks, followed by 3-monthly testing in the longer term.[50–52]

TPMT activity in human tissue is under the control of a common genetic polymorphism.[49] Therefore, TPMT activity can be assessed either by the activity of TPMT and 6-thioguanine levels in the serum or by the genetic polymorphism of TPMT. There are only a few studies from Asia (Korea, India, China, Japan, and Singapore) on the polymorphism of TPMT.[51,54–57] Prospective studies evaluating dose optimization based on measurements of TPMT, 6-thioguanine, or 6-MP levels to monitor clinical response are still lacking. It remains uncertain whether this strategy provides substantial incremental benefit to the traditional routine of monitoring complete blood count, liver-associated laboratory parameters, and clinical response.

Statement 35

Patients receiving systemic corticosteroids should also be prescribed calcium supplementation and vitamin D.

Level of agreement: a—42%, b—42%, c—16%, d—0%, e—0%
Quality of evidence: III
Classification of recommendation: C

Corticosteroids impair osteoblast function, induce osteoblast apoptosis, reduce intestinal calcium absorption, and increase renal excretion of calcium.[58] Patients on glucocorticoids are at increased risk for fracture, with the greatest bone loss occurring in the initial months of treatment.[59–61] A Cochrane analysis of 5 clinical trials in 274 patients showed that vitamin D and calcium supplementation demonstrate clinically and statistically significant prevention of bone loss at the lumbar spine and forearm in patients treated with corticosteroids.[62] It is therefore recommended that patients taking corticosteroids should be prescribed with calcium and vitamin D supplements. The recommendation for younger men and premenopausal women is a daily intake of elemental calcium of 1000 mg, either from diet or by supplementation. Men and women over 50 years of age require 1500 mg of calcium. Vitamin D intake of 400–800 IU/day should be adequate for relatively healthy individuals, but housebound patients with intestinal malabsorption may require a higher amount.[62]

Biological agents. TNF alpha inhibitors are increasingly used in the Asia–Pacific region, typically in patients failing conventional therapies or who are steroid dependent. Infliximab, adalimumab, and certolizumab have all demonstrated efficacy in CD. Careful patient selection, monitoring, and patient education are mandatory to maximize the benefit of these drugs and to minimize adverse effects. Regular patient follow-up by a gastroenterologist familiar with anti-TNF therapy is recommended. Opportunistic infection can occur, especially given the higher background prevalence of TB and hepatitis B virus (HBV) infection in parts of the Asia–Pacific region, and vaccination and infection screening prior to therapy is important. Newer and more specific biological agents will likely be available in the future.

Statement 36

The indications for biological agents include failure of conventional therapy in luminal disease [I-A], as well as fistulizing CD [I-A], perianal fistulizing CD in conjunction with appropriate surgical management, and treatment of some extra-intestinal manifestations [II-3,B].

Level of agreement: a—47%, b—53%, c—0%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

Infliximab and adalimumab are anti-TNF agents approved for the induction of remission and maintenance of remission in refractory CD and fistulizing CD.[63–67] Certolizumab has not been widely used in the Asia–Pacific region. There are, as yet, no head-to-head trials on currently approved biological agents. Patients given infliximab early in the course of CD have higher response rates than those with longer disease durations supporting their earlier use if possible.[68]

In the treatment of fistulizing CD, infliximab has response and remission rates of 69% and 49%, respectively, following a three-dose induction regimen.[69] Overall, infliximab maintenance therapy reduces hospitalization and surgery in fistulizing CD.[70] Post-hoc analyses demonstrated efficacy of adalimumab in fistulizing CD with closure of fistulae maintained at 1 year.[64] The efficacy of anti-TNF agents in the induction and maintenance of remission in fistulizing CD was confirmed in a meta-analysis that pooled data from 21 trials in over 5000 patients.[29]

Data from Western and Asian populations indicate that CD is a progressive condition that leads to cumulative complications over time.[71] As such, the treatment paradigm is no longer limited to symptomatic improvement but to induction of sustained steroid-free remission with mucosal healing.[72] Bone mineral density and extra-intestinal manifestations may improve following treatment with anti-TNF agents.[73–75] In cohort studies, infliximab reduced postoperative endoscopic recurrence of CD.[76,77]

Statement 37

Combined infliximab and thiopurine is more effective than either alone in thiopurine-naïve patients [I-A]. The risk-benefit balance, including the risk of lymphoma and opportunistic infections, needs to be considered [II-3, B].

Level of agreement: a—47%, b—53%, c—0%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

Combined anti-TNF therapy with a thiopurine may be more effective than used alone in the treatment of CD. In a large randomized study, the steroid-free remission rate at week 26 in patients with moderate-to-severe CD was significantly higher (57%) in those receiving combination therapy compared with AZA alone (30%) or infliximab alone (44%).[78] In patients stabilized on thiopurine and infliximab, randomized withdrawal of AZA significantly reduced median trough levels of infliximab and increased CRP levels.[79] These biological parameters support the benefits of thiopurine co-therapy with anti-TNF treatment.

Hepatosplenic T-cell lymphoma, a rare lymphoma associated with the use of thiopurines and anti-TNF agents,[80] has been previously described in Asian non-IBD populations.[81] As yet, few studies support the use of methotrexate co-therapy with anti-TNF agents, but this may be appropriate in those who are unable to use, or intolerant of, thiopurine therapy.

Statement 38

Infliximab is given at a dose of 5 mg/kg IV infusion at weeks 0, 2, 6 for induction of remission and 8-weekly thereafter for maintenance of remission. Adalimumab is given at a dose of 160 mg SC at week 0 and 80 mg SC at week 2 for induction, then 2-weekly thereafter.

Level of agreement: a—53%, b—47%, c—0%, d—0%, e—0%
Quality of evidence: I
Classification of recommendation: A

The induction regimen of three doses of infliximab is superior to a single-dose regimen. Similarly, scheduled 8-weekly maintenance therapy is superior than episodic treatment.[29,65] Episodic therapy with infliximab on relapse is less efficacious than regular maintenance therapy and associated with the formation of antibodies to infliximab (ATI). In the ACCENT I study, response was seen in 58% of participants receiving induction infusions at 30 weeks, and 45% of these achieved clinical remission.[65] Real-life long-term follow-up studies have similarly demonstrated excellent safety and durable efficacy.[82]

In clinical trials, induction therapy with adalimumab achieved a response in 58% of patients, with 52% achieving ongoing response, and with a 40% remission rate at 1 year.[64,83] An induction regimen of 160 mg and then 80 mg 2 weeks later is superior to an 80 mg/40 mg regimen.[83] Certolizumab pegol has also demonstrated efficacy for inducing and maintaining remission,[84,85] but is not yet widely available in the Asia–Pacific region.

Statement 39

Screening and treatment for active/latent infection with Mycobacterium tuberculosis *and other infections should be carried out prior to commencing anti-TNF treatment.*

Level of agreement: a—79%, b—21%, c—0%, d—0%, e—0%
Quality of evidence: II-3
Classification of recommendation: B

Anti-TNF agents increase the risk of opportunistic infections. Postmarketing reports identified a fourfold increase in the risk of TB infections, typically reactivation of latent TB.[86] Screening for TB prior to commencing anti-TNF therapy reduces the rate of TB by 74%.[87] TB risk assessment should include a history of TB contact, a chest X-ray, an interferon gamma release assay (such as QuantiFERON-TB Gold assay that does not react against Bacillus Calmette–Guérin (BCG) vaccination) or tuberculin skin test (> 1 cm Mantoux wheal).[88] Patients starting anti-TNF therapy should be advised to avoid known contacts with TB, if possible, and to present for urgent medical attention if they develop signs of sepsis, and to follow these precautions for at least the duration of immunosuppressive therapy. Isoniazid prophylaxis can be considered for those at high risk of acquiring TB once on anti-TNF treatment.

Statement 40

Screening for hepatitis B virus (HBV) infection is recommended prior to initiation of immunosuppressive agents. Antiviral prophylaxis should be considered in HBV-positive

individuals receiving biological agents or steroids [II-3, C]. Patients should be up-to-date with specific vaccinations. Live virus vaccinations are to be avoided for at least 3 weeks prior to commencing a biological agent and 3 months after the last dose of the biological agent [II-3, C].

Level of agreement: a—61%, b—39%, c—0%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

Prior to the start of immunosuppressive therapy, prophylaxis against several pathogens including pneumococcal, influenza, varicella zoster virus (VZV), human papilloma virus (HPV) and HBV is generally recommended.[89–91] In the Asia–Pacific region, the higher prevalence of HBV infection requires increased awareness of potential reactivation of HBV replication with the use of immunosuppressive therapies. Icteric flares with hepatic decompensation and fatal hepatitis have been reported with immunosuppression.[90] Screening for HBV (HBsAg, HBsAb, HBcAb) is recommended for CD patients, ideally at the time of diagnosis preceding the commencement of immunosuppressive therapy. Patients negative for HBV should be vaccinated against HBV. Seropositive HBV patients (HBsAg) should be considered for prophylactic antiviral treatment prior to commencement of anti-TNF therapy or steroids as TNF is a central mediator of the anti-HBV response. HbcAb-positive/HbsAg-negative patients do not require routine HBV prophylactic treatment, but periodic monitoring of HBV-DNA levels is recommended. Antiviral prophylaxis is recommended for the duration of anti-TNF treatment and for up to 6 months after completion.[92] Patients with HBV on immunomodulator monotherapy require monitoring for HBV reactivation; antiviral therapy can be used for virus reactivation.

Live virus vaccinations may result in potentially fatal overwhelming infection in the setting of immunosuppression and must be avoided 3 weeks prior to the commencement of an anti-TNF drug and for 3 months after the last dose of biological agents.[93] Examples of live vaccines include the measles–mumps–rubella, live oral polio, yellow fever, oral typhoid, live-attenuated influenza, BCG, and varicella vaccines. Nonlive vaccines are generally considered safe to use and they include diphtheria, tetanus, acellular pertussus, inactive polio, inactivated influenza, pneumococcal, hepatitis A and B, parenteral typhoid, meningococcal, oral killed cholera, inactivated Japanese encephalitis, HPV, and inactive tick-born encephalitis vaccines.[90]

Statement 41

Contraindications for anti-TNF therapy include congestive cardiac failure (NYHA Class III and IV) and demyelination disorders [II-3, C]. There are limited data on the use of anti-TNF agents during pregnancy but they appear to be safe [II-3, C].

Level of agreement: a—83%, b—17%, c—0%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

Anti-TNF therapy is contraindicated in patients with New York Heart Association (NYHA) class III or IV heart failure due to an increased risk of death observed in heart failure clinical trials.[94] Neurological adverse effects from anti-TNF have been reported, including case reports of central and peripheral demyelination. Variable outcomes have been demonstrated on anti-TNF treatment withdrawal.[95] Cumulative data support the safety of anti-TNF treatment during pregnancy in both the rheumatology and inflammatory bowel diseases (IBD) literature, with expected versus observed outcomes among women exposed to infliximab similar to the general population.[96] The United States Food and Drug Administration recognizes anti-TNF agents as category B drugs. Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Infliximab and adalimumab as IgG antibodies cross the placenta and drug levels may remain detectable in an infant's serum for up to 7 months after birth.[97] Passively transferred immunosuppression from *in utero* exposure to infliximab has resulted in infant fatality from disseminated BCG infection.[98] Live vaccinations must be avoided in infants exposed to anti-TNF *in utero* until they are at least 7 months of age.

Statement 42

In patients who enter clinical remission, anti-TNF may be given long-term [II-3, C]. Ongoing monitoring of clinical efficacy and complications is recommended at least 3–6 monthly [II-3, C]. Scheduled maintenance therapy is recommended rather than episodic therapy [II-1, B]. Cessation of anti-TNF may be an option [II-3, C].

Level of agreement: a—37%, b—58%, c—5%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

Anti-TNF therapy has been shown to maintain remission with scheduled maintenance therapy.[64,65] Scheduled maintenance infliximab resulted in higher rates of mucosal healing compared with episodic treatment.[99] Episodic treatment risks disease relapse, especially in patients who previously failed immunomodulator therapy. However, infliximab induction can successfully bridge toward immunomodulator maintenance in immunomodulator-naïve patients.[100] Repeat exposure to a biological agent after a drug holiday also carries a risk of delayed hypersensitivity allergic reactions.[66] In Asia, scheduled maintenance therapy with infliximab has been adopted.[101]

Currently, there are insufficient data to make recommendations on when or how to stop anti-TNF therapy in those in remission, and certainly, the risks and benefits of this approach must be discussed with the patient on a case-by-case basis. Current evidence suggests that stable remission following discontinuation of infliximab is most likely in those without biological indicators of disease activity, that is with normal levels of CRP and endoscopic evidence of mucosal healing.[102] Bridging of the anti-TNF agent to an alternative treatment such as thiopurine or surgery may be an option. The use of infliximab for induction of remission bridging across to AZA or mercaptopurine is most effective for those naïve to, or who have not previously failed, thiopurine therapy. A high rate of loss of efficacy can be expected in those who previously failed thiopurine therapy.[100]

Statement 43

Limited data are available at present on the use of anti-TNF antibody titres and anti-bodies to anti-TNF agents to optimise treatment or to explain primary non-response or secondary loss of response to anti-TNF agents.

Level of agreement: a—72%, b—28%, c—0%, d—0%, e—0%
Quality of evidence: II-3
Classification of recommendation: B

Assessing levels of antichimeric-human antibodies such as ATI and measuring trough drug concentrations of anti-TNF in the blood have been proposed to help explain suboptimal treatment response or to explain primary nonresponse or secondary loss of response to anti-TNF agents.[103] So far, this has not been widely adopted in the Asia–Pacific region.

Statement 44

Primary non-response to anti-TNF usually requires a change of treatment or re-evaluation of symptoms.

Level of agreement: a—72%, b—28%, c—0%, d—0%, e—0%
Quality of evidence: II-3
Classification of recommendation: C

Reasons for nonresponse or loss of response to anti-TNF treatment include noninflammatory CD strictures, other mechanical complications, dietary intolerances, and irritable bowel syndrome. Elective or premature switching of anti-TNF agents may result in unnecessary loss of drug efficacy.[104] Evaluation for the reasons for ongoing symptoms may require comprehensive clinical assessment that includes radiological investigations and/or ileocolonoscopy plus determinants of inflammatory activity such as CRP and fecal calprotectin. When primary nonresponse is confirmed, an alternative anti-TNF agent may be tried.

Secondary loss of response to anti-TNF treatments occurs at a rate of 13% per year of treatment.[105,106] Escalation of treatment may be an option for patients to re-enter remission,[105] either by increasing the dose of anti-TNF, decreasing the interval between doses, temporary steroid co-therapy, and commencement, change or optimization of immunomodulator dosage. Infliximab dose can be increased to 10 mg/kg[65] and adalimumab dose interval decreased from every other week to weekly.[107] Surgical management should be considered.

Statement 45

At present, there is no definite role of anti-mycobacterial avium paratuberculosis (MAP) therapy in patients with CD.

Level of agreement: a—83%, b—17%, c—0%, d—0%, e—0%
Quality of evidence: II-2
Classification of recommendation: B

MAP has been detected in the tissues and blood of CD patients more frequently than in those without CD.[108] Trials of antituberculous therapy for maintenance of remission in CD provided mixed results.[109,110] A randomized Australian study comparing clarithromycin, rifabutin, and clofazimine with placebo found no significant difference in the rate of CD relapses between the antibiotic-treated and control groups at the 1-year follow-up.[111]

Statement 46

Nutrition and osteoporosis are important considerations in the long-term management of CD. Medication use and surgical options should take into consideration fertility, pregnancy and breastfeeding.

Level of agreement: a—83%, b—17%, c—0%, d—0%, e—0%
Quality of evidence: III
Classification of recommendation: C

Malnutrition of both macro- and micronutrients is common in CD.[112] Anemia is common in IBD through iron deficiency and anemia of chronic disease. Anemia assessment should consider the possibility of drug-induced anemia secondary to AZA, 6-MP or sulfasalazine, and folate and vitamin B_{12} deficiencies. At least annual hemoglobin and iron studies are recommended, along with nutritional assessment and advice, most appropriately by a dietitian.

The frequency of miscarriage, preterm deliveries, cesarean sections, or congenital abnormalities, and the average infant birth weight is no different in patients with CD compared with non-IBD controls,[113,114] although a meta-analysis found that IBD increased the risk of having a small or premature baby.[115] Older age at the time of conception was associated with congenital abnormalities and preterm delivery; and smoking increased the risk of preterm delivery.[113,114] Although fertility in inactive IBD is generally unaffected, active disease, pelvic surgery, or sepsis can decrease fecundity.

Difficult CD cases require combined antenatal management by experienced obstetricians and IBD-focused clinicians. Conception should ideally take place during remission with folate supplementation and optimization of nutritional status. Patients with acute severe disease or other life-threatening complications of CD should be managed as for the nonpregnant patient. In general, the mode of delivery is best guided by obstetric indications rather than CD. However, patients with perianal CD or ileo-anal pouch formation should be strongly considered for cesarean section to avoid the risk of damage to the anal sphincter. Absolute indications for surgery are unaltered by pregnancy, and surgery should only be delayed where aggressive medical therapy may affect critical fetal maturation.[116]

Surgical perspectives in the management of CD. CD is prone to recurrence and cannot be cured surgically. Bowel conservation to maintain adequate digestive and absorptive function is a key therapeutic objective, and surgery should be employed only for the management of complications. Four contentious areas of surgical management are highlighted and are presented as consensus statements:

Statement 47

Crohn's disease with dysplasia-associated lesions or masses (DALMs) and high-grade dysplasia of the colon and/or rectum that cannot be safely resected endoscopically should undergo surgical resection.

Level of agreement: a—77%, b—22%, c—6%, d—0%, e—0%
Quality of evidence: III
Classification of recommendation: C

Patients with long-standing, extensive Crohn's colitis are at increased risk of colorectal cancer.[117] Endoscopic surveillance is recommended every 1–2 years after 8 years of Crohn's colitis when disease affects at least a third of the colon. Any stricture and mass lesions must be biopsied. Flat, high-grade dysplasia has been considered a strong indication for colectomy because of its association with synchronous or metachronous adenocarcinoma.[118,119] Our consensus opinion is that patients with long-standing disease who are found to have high-grade dysplasia or multifocal low-grade dysplasia should be considered for colectomy when these findings are confirmed by two independent gastrointestinal pathologists with experience in IBD.[118,119] Our opinion is that unifocal low-grade dysplasia does not pose the same risk and colectomy in this situation is not recommended.

A dysplastic mass that cannot be resected endoscopically is a strong indication for colectomy, especially in medically fit patients with long-standing colitis, primary sclerosing cholangitis, and a family history of colorectal cancer.[120–123] The use of chromoendoscopy may improve identification of flat dysplasia.[124]

Statement 48

Patients with long-standing small bowel Crohn's disease should undergo biopsies of small bowel strictures at the time of stricturoplasty.

Level of agreement: a—67%, b—33%, c—0%, d—0%, e—0%
Quality of evidence: III
Classification of recommendation: C

Symptomatic strictures in the small bowel presenting with obstruction often require surgical intervention. Stricturoplasty, rather than resection, is often preferred to conserve bowel length. Epidemiological data and case reports suggest that CD patients have a 3- to 100-fold increased risk of small bowel cancer.[125–132] CD small bowel strictures should be biopsied intraoperatively at the time of stricturoplasty to exclude cancer.

Statement 49

a) Patients who require surgery for isolated rectal disease may undergo proctectomy with creation of a stoma. Those with concomitant colonic disease can be considered for procto-colectomy.

b) Restorative procto-colectomy with ileopouch anal anastomosis can be considered in an experienced tertiary center if the small bowel is unaffected and there is no perianal disease provided patients are counseled on the long-term risks of pouch failure.

Level of agreement: a—50%, b—44%, c—6%, d—0%, e—0%
Quality of evidence: III
Classification of recommendation: C

Patients with poorly responsive proctitis and intractable symptoms should undergo proctectomy with end-colostomy. More extensive involvement of the colon in addition to the rectum warrants a procto-colectomy with an end-ileostomy. Although considered the procedure of choice in ulcerative colitis, the creation of ileal pouch-anal anastomosis (IPAA) is controversial in CD. A confirmed diagnosis of CD generally precludes IPAA as a reconstructive option because of the reported poor outcomes.[133–136] Melton *et al.*,[137] however, found that pouch loss rates are low, and functional results can be favorable in CD patients with IPAA, provided the diagnosis of CD is established preoperatively or immediately following surgery. Outcomes in patients with delayed diagnosis of CD after the creation of an IPAA appeared to be worse. Despite that, up to half of these patients retained their pouches at 10 years, suggesting that selected cases can be stoma-free for a significant number of years. The decision to perform an IPAA in the presence of Crohn's colitis should only be undertaken at a tertiary center with the necessary expertise from a multidisciplinary team.[138] In addition, contraindications such as the presence of perianal-fistulizing disease and the presence of small bowel CD activity preclude IPAA.[139,140]

Statement 50

Complex Crohn's perianal fistula may be treated by long-term draining setons. Combined treatment with biological therapy may allow removal of setons with healing in some cases [II-2, B].

Level of agreement: a—47%, b—53%, c—0%, d—0%, e—0%
Quality of evidence: II-2
Classification of recommendation: B

CD perianal fistulas should be managed conservatively unless they are symptomatic. A perianal abscess should always be surgically drained. An asymptomatic simple fistula may be observed. Long-term indwelling seton, which does not negatively impact fecal continence, is an effective management modality for complex perianal Crohn's fistulas if a significant amount of sphincter muscle is involved.[141] The use of seton placement and concomitant infliximab maintenance therapy for perianal-fistulizing CD can promote fistula closure and allow for eventual removal of setons.[142]

Perianal fistula

Statement 51

It is important to determine if Crohn's disease-related perianal fistula is simple or complex using either pelvic MRI, endoanal ultrasound and/or examination under anaesthesia [II-2, B]. All such patients should be evaluated for disease activity in the colon and terminal ileum [III, C].

Level of agreement: a—100%, b—0%, c—0%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

Fistulas can be either perianal or nonperianal, such as a fistula communicating with other viscera (vesicoenteral), loops of

intestine (enteroenteral fistula), or the abdominal wall (enterocutaneous fistula). In the natural history of CD, the cumulative risk of developing a perianal fistula is approximately 10% at 1 year, 15% at 5 years, and 20% at 10 years. Perianal fistulas occur more often when there is CD involvement of the colon and the rectum.[143,144]

Treatment of perianal fistulas depends upon the location and nature of the fistula (simple or complex), presence of abscess, and the severity of the intestinal disease. A careful examination of the perianal area can help to classify the fistula type as either simple or complex.[145] A simple fistula is superficial and lies below the dentate line, has a single external opening, has no pain or fluctuation to suggest perianal abscess, and has no evidence of a rectovaginal fistula, or anorectal stricture. A complex fistula is high (i.e. fistula tract origin is high intersphincteric, high transsphincteric, extrasphincteric or suprasphincteric), may have multiple external openings, and/or be associated with a perianal abscess, recto-vaginal fistula, anorectal stricture, or active rectal disease.[146]

Perianal fistulas may be investigated with pelvic MRI, anorectal endoscopic ultrasonography (EUS), or examination under anesthesia (EUA). In the hands of expert surgeons, EUA is considered the gold standard.[147] EUA has an accuracy of 90% for diagnosis and classification of fistulas and abscesses, and concomitant surgical incision and drainage of abscesses with seton placement may be conducted at the same time. MRI has an accuracy of 76–100% for the diagnosis and classification of perianal fistulas.[148] MRI is the initial diagnostic technique of choice and provides useful cross-sectional imaging.[149] EUS offers a diagnostic accuracy of between 56% and 100%.[150]

Statement 52

a) An asymptomatic simple perianal fistula may be observed. A symptomatic simple perianal fistula should be treated with antibiotics [III, C]. Fistulotomy should be avoided in complex fistulas but may be an alternative in simple fistula. [in text]
b) Complex perianal fistulas should be treated with an anti-TNF agent [I, A] with or without antibiotics [II-3, C]. Thiopurines can be used concomitantly [III, C]. Perianal abscess, if present, should be expediently drained [III, C].

Level of agreement: a—45%, b—55%, c—0%, d—0%, e—0%
Quality of evidence and Classification of recommendation: as above

While asymptomatic simple perianal fistulas may be observed, a symptomatic fistula requires treatment. Antibiotics with either metronidazole (750–1500 mg/day) or ciprofloxacin (500–1000 mg/day) remain the mainstay of treatment for simple perianal fistula.[151,152] Treatment duration is for 3–4 months. AZA and 6-MP are effective in treating CD perianal fistulas. In a meta-analysis of five controlled studies, a response (defined as complete closure or decreased drainage) was seen in 54% of the patients treated with AZA or 6-MP compared with 21% in the placebo group (OR: 4.44; 95%CI 1.50–13.2).[152] A combination of AZA and antibiotics has been found to have a better response rate.[151]

Conclusions

These are the first Asia–Pacific consensus statements on CD developed through a rigorous process according to the Delphi system and taking into account evidence from the literature, local/regional research, and input from a multidisciplinary panel of experts from the Asia Pacific Association of Gastroenterology Working Group on IBD. These statements complement the previously published Asia–Pacific Consensus Statements on ulcerative colitis.[153] Although these statements were designed for the entire region, the Working Group recognizes the diversity within Asia–Pacific and recommends that the consensus statements are customized to the needs of each specific country. Broadly, the region can be divided into the Westernized populations of Australia and New Zealand where there is a high incidence of CD, the developing regions of southeast Asia characterized by increasing affluence and a rapidly rising incidence of CD, and the regions that remain relatively underdeveloped with few cases of IBD. These consensus statements aim to harmonize definitions and provide recommendations on diagnosing and managing CD, and to improve reporting for clinical and research purposes. Data from Asia show an increasing CD incidence over recent decades, emphasizing the importance of environmental factors in the pathogenesis of IBD. There are research opportunities in further studying the interaction between genes and the environment in this, the most populous, region of the world. In addition, these consensus statements emphasize the specific needs of the Asia–Pacific region with regard to testing for HBV, differential diagnosis of TB, and managing TB in the setting of immunosuppressive medications. The use of biological agents, which are now integral to the management of CD, requires exclusion of and careful monitoring for opportunistic infections. Future updates are required to ensure ongoing relevance and accuracy in times ahead.

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