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POSITION PAPER ON THE USE OF DRUG THERAPIES IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

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Abstract

Several new classes of drugs have recently been developed for the management of Inflammatory Bowel Disease (IBD). In response, updated international guidelines have been published providing recommendations on how to incorporate these agents into existing treatment algorithms. Recent approval of these new therapies in South Africa has however raised many questions on how they should best be used in a local setting. Since no formal guidance is available, the South African Gastroenterology Society (SAGES) has put forward, in the present position paper, guidance on the best use of both existing and novel drug therapies in the management of IBD in the South African setting.

Introduction

The term inflammatory bowel disease (IBD) refers by and large to two chronic disorders of the gastrointestinal tract, Crohn's disease (CD) and ulcerative colitis (UC). Both conditions are progressive and destructive, often require surgery, and negatively impact quality of life. Ultimately IBD is responsible for considerable health care expenditure. Historically, the management of IBD involved the use of oral and topical 5-aminosalicylates (5-ASAs) and immunomodulators (IMMs) in the form of azathioprine, 6-mercaptopurine, and methotrexate.[1-6] Unfortunately, these agents fail to alter the natural history of IBD to any great degree.

With the development of anti-tumour necrosis factor (anti-TNF) drugs two decades ago it became possible for the first time to significantly improve IBD outcomes, and these monoclonal antibodies have revolutionised the management of moderate to severe UC and CD. There are currently three anti-TNFs approved in South Africa for the treatment of IBD: infliximab, adalimumab, and golimumab. They all target the cytokine TNF-alpha which is the key inflammatory cytokine in the pathogenesis of both UC and CD.[1-6]

However, treatment failure is seen in a significant proportion of patients treated with anti-TNFs. Approximately 30% of patients will not respond to initial treatment (primary non-response), and 40% of those who initially respond will lose response at some point in the course of the disease (secondary loss of response). In addition, anti-TNF drugs carry the risk of serious adverse effects, the most important in South Africa is tuberculosis. As such there has been a plethora of research investigating therapies with different mechanisms of action to address the unmet need in the management of IBD. Over recent years, several new classes of drugs have been developed and approved for the management of IBD.[1-6] Two of these agents have recently received approval in South Africa for use in IBD. The first is ustekinumab, which targets interleukin 12 and 23; cytokines pivotal in the pathogenesis of IBD. The second vedolizumab, blocks the interaction of α4β7integrin on the surface of circulating white blood cells

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with its corresponding adhesion molecule MADCam on the gut endothelium, essentially inhibiting leucocyte trafficking into the gut mucosa. Following development of these newer biologics, several international guidelines have recently been published.[1-6] These focus on populations very different from ours in South Africa. The recent approval of these new therapies in SA has raised a number of questions on how they should best be used in a local setting such as ours. To date there has been no formal guidance in SA.

Scope and purpose of this position statement on the management of IBD in South Africa

The overall objective is to improve the medical management of patients with IBD in a local setting, addressing new and existing therapies, and providing strategies to optimise their use in clinical practice. The health questions addressed are specifically for patients with IBD and the target population is patients with IBD who are managed at district, regional and tertiary hospitals. Only medications currently approved in South Africa are addressed in this document

Methods

1. Stakeholder involvement

The position statements in this document were developed by IBD experts from SAGES and the Gastroenterology Foundation of sub Saharan Africa and included representation from all academic Gastroenterology divisions in SA, as well as representatives from the Private sector.

2. Rigour of development

The position statements in this document are based on the available literature and includes expert opinion. Recently published international guidelines were used as a template and all recommendations in this document concur with their suggestions.[1-6] A working group met in Cape Town in February 2020. Experts from all the mentioned stakeholders were invited to participate. Prior to the meeting each expert was tasked with answering key questions, following a detailed review of the literature. A draft document was then compiled and forwarded to all participants. The proposed position paper was then discussed in detail by those present and the content was modified with a 100% consensus.

3. Editorial independence

Funding for the development of these guidelines was obtained from SAGES. Takeda SA sponsored the meeting logistics. There was no participation by any pharmaceutical company. Conflicts of interest are reported below.

Sections

5-aminosalicylates (5-ASA) in IBD

1. 5-ASA agents in Crohn's disease

5-ASA should not be used for either the induction or maintenance of remission in patients with Crohn's disease.

In general, 5-ASAs have not been shown to be effective in the management of CD.[1-3,8,9] Sulphasalazine may however have some benefit in a sub-group of patients with mild colonic CD and a trial of therapy can be used in this clinical scenario.[1]

2. 5-ASA agents in ulcerative colitis

Oral and topical 5-ASAs are considered first line therapy for mild to moderately active UC. The choice of oral or topical therapy, or the use of both in combination, depends on the extent and activity of the disease.[3-7]

2.1 5-ASAs for the induction of remission in patients with active ulcerative colitis

1. For isolated proctitis, rectal 5-ASA therapies at a dose of 1 g/d is recommended.

A meta-analysis of 38 studies of active proctitis or left sided UC found that rectal 5-ASA was superior to placebo for both symptomatic and endoscopic remission. There were no significant differences with regards to dose (1 or 4 g/day) or formulation (liquid, gel, foam, or suppository).[10]

2. If rectal 5-ASA is not adequate to control active proctitis, oral 5-ASAs can be used in addition.

3. In more extensive colitis, oral 5-ASA (at a dose of at least 2 g/day) is recommended.

A meta-analysis of 11 randomised controlled trials of patients with UC treated with oral 5-ASAs demonstrated superiority of 5-ASAs in inducing remission compared with placebo.[11]

4. Combining oral 5-ASA and rectal 5-ASA therapies confers additional benefit over either alone.

In left-sided UC, a meta-analysis of four randomised controlled trials using a combination of rectal 5-ASA enemas (1 g/day) combined with oral 5-ASAs (at least 2 g/day) was more effective than oral 5-ASA alone for induction of remission.[12] Patients with extensive UC also appear to benefit from combination therapy.[13]

5. Low dose oral 5-ASA (2-2.4 g/day) is preferred wherever possible over higher doses (4-4.8 g/day) in mildly active ulcerative colitis, as there is no difference in remission rates.

In a recent meta-analysis, a low dose of 2–2.4 g/day of 5-ASA was found to be just as effective as a higher dose (4.8 g/day) (RR, 0.91; 95% CI, 0.85–0.98). A subgroup analysis indicated that patients with more active (moderate) UC may benefit from the higher dose of 4.8 g/day.[14]

6. Once daily dosing is as effective as split dosing and is likely to improve adherence.[15]

7. There are no differences in the various 5-ASA formulations in terms of efficacy. In patients who fail to reach remission with appropriately dosed 5-ASA therapy, changing to an alternate 5-ASA formulation is not recommended to induce remission.

Several meta-analyses have not shown any therapeutic differences between different 5-ASA formulations.[16,17]

8. Patient preference for the type of formulation (such as tablet size) should be taken into consideration.

There is little to choose between the different formulations of 5-ASA in terms of efficacy, and the best drug should be selected taking into account patient preference for formulation

(for instance granules or tablets, tablet size and number required daily), in order to maximise treatment adherence and considering cost.[18] Patients may develop side effects to sulphasalazine, and if so will need to switch to a sulpha-free mesalazine product.

9. Additional therapy is usually required to induce remission in moderate to severely active ulcerative colitis as 5-ASA monotherapy is unlikely to be sufficient.[3-7]

2.2 Maintenance of remission in patients with ulcerative colitis

1. In ulcerative proctitis rectal 5-ASA at a dose of 1 g/day is recommended to maintain remission.[19]

2. In patients with more extensive ulcerative colitis oral 5-ASA therapy (at least 2 g/day) as well as rectal 5-ASA therapy is recommended.

Maintenance 5-ASA therapy is recommended to decrease the risk and frequency of flares. A recent Cochrane analysis demonstrated greater efficacy with higher doses (2 g/day or more).[20]

3. In patients on biologic therapy who have previously failed 5-ASAs, concomitant use of 5-ASA agents is not recommended.

Several large studies have recently demonstrated that discontinuing 5-ASA in patients with UC starting anti-TNF therapy did not increase the risk of adverse clinical events.[21,22]

4. It is not clear whether concomitant use of 5-ASA agents with anti-TNFs or thiopurines has additional benefit in maintaining remission in patients who have not failed 5-ASAs.[23]

Corticosteroid use in IBD

1. In both Crohn's disease and ulcerative colitis, corticosteroids should be used for the induction of remission only; they are not indicated for maintenance therapy because of lack of efficacy and adverse effects.

In patients with IBD in whom remission is achieved with corticosteroids, immunomodulators should be considered as maintenance therapy. In those unresponsive to corticosteroids, escalation to more effective therapies such as biologics and immunomodulators should be considered.[1-7]

2. All patients treated with systemic corticosteroid should receive a calcium and vitamin D supplement.

3. Corticosteroid use in ulcerative colitis for the induction of remission

1. Topical rectal corticosteroids are indicated in patients with limited ulcerative colitis or ulcerative proctitis who are intolerant of or refractory to mesalazine therapy.

Four RCTs compared rectal corticosteroids (three trials of budesonide foam 2–4g/day, one trial of budesonide enema) with placebo for the induction of remission in patients with mild to moderate ulcerative proctosigmoiditis, treated for 4 weeks. On meta-analysis, rectal corticosteroid therapy was significantly more effective than placebo for inducing remission (RR, 0.73, 95% CI 0.66–0.80). In a single trial comparing budesonide foam with hydrocortisone foam, there was no difference in efficacy.[24] Suppositories may be more effective for proctitis while enemas or foams are preferable in more extensive left sided disease.

2. Systemic corticosteroid therapy is recommended in patients with moderate to severe disease activity and in those with mild activity who do not respond to optimal 5-ASA therapy regardless of the extent of disease.

The threshold for the introduction of oral corticosteroids in patients with mild to moderate UC depends upon the response to and tolerance of 5-ASA, patient's preference and the physician's practice. Dosing at 1 mg/kg is recommended and doses higher than 60 mg/day do not appear to confer additional benefit. Courses should be tapered over 8–12 weeks.[3-7]

Colonic release budesonide MMX 9 mg/day may be considered in patients with mild to moderate disease who are intolerant or refractory to 5-ASA, however this is not available in SA. In contrast to budesonide MMX, oral non-MMX budesonide does not appear to be effective in the treatment of UC.[25,26]

3. Intravenous hydrocortisone and methylprednisolone are considered first line therapy in acute severe ulcerative colitis (see Section 9).

4. Corticosteroid use in Crohn's disease in the induction of remission

1. Controlled ileal release budesonide is indicated as first line therapy in mild to moderately active ileocaecal Crohn's disease.[1-3]

In a randomised double-blind trial, budesonide 9 mg was found to be as effective as prednisolone 40 mg daily at 8 weeks in inducing remission in patients with mild to moderate ileocaecal CD at 51% and 52.5%, respectively, and with much fewer side effects.[27]

2. Patients with more extensive or severe Crohn's disease should be treated with systemic corticosteroids.[1-3]

Doses higher than 60 mg/day do not appear to confer additional benefit. Courses should be tapered over 8–12 weeks. The role of topical corticosteroids in the treatment of Crohn's colitis is unclear.

3. Patients with severe Crohn's disease requiring admission should be treated with intravenous corticosteroids.[1-3]

Immunomodulators in IBD

In this position paper the term immunomodulators refers to azathioprine, 6-mercaptopurine, and methotrexate.

1. Immunomodulators in ulcerative colitis

1.1 Thiopurines in ulcerative colitis (6-mercaptopurine (6MP) and azathioprine)

Dosing is usually weight based at 2–2.5 mg/kg for azathioprine and 1–1.5mg/kg for 6MP.[3] Genetic polymorphisms of thiopurine methyltransferase (TPMT) indicate that both the response and risk of side effects vary between patients. TPMT testing should be considered before the initial use of azathioprine or 6MP to treat patients with IBD. Monitoring of thiopurine metabolites is not available in SA.

Patients should be advised to use sunscreen and be monitored for skin cancers, and females should undergo regular PAP smears.[27,28] It is important to be aware of the risk of lymphomas especially in young males and older patients.[3,29]

1. Thiopurines are not indicated for induction of remission in patients with active ulcerative colitis.

Based on the slow onset of action of thiopurines, they are not effective as monotherapy for the induction of remission in patients with active disease, in the absence of

corticosteroids.[3-6]

2. Thiopurines are effective in the maintenance of remission and should be considered in patients who are inadequately controlled on maximum 5-ASA therapy, those who are intolerant of 5-ASAs, or those who are steroid dependent or resistant on maintenance therapy.
There are multiple studies and several meta-analyses reporting superiority of thiopurines over placebo in the maintenance of steroid induced remission but not in the induction of remission. The number-needed-to-treat (NNT) to prevent one disease recurrence is five.[3-7,30-37]

3. Thiopurines may be indicated in combination with certain biologics in order to reduce antibody formation.
Data from the SUCCESS study suggest that the combination of azathioprine with infliximab is better than monotherapy.[3]

4. The high risk of relapse following the discontinuation of thiopurines should be considered before choosing to discontinue these agents.
The average time to relapse is 18 months and almost 40% will relapse within 3 years.
This is more likely in those with extensive UC and with evidence of disease activity at the time of discontinuing these drugs.[39]

2. Methotrexate
Studies do not support the use of methotrexate for the treatment of ulcerative colitis. It may however be of use in combination with a biologic to prevent antibody formation.[3,40,41]

2. Immunomodulatory therapy in Crohn's disease
2.1 Thiopurines in Crohn's disease
The recommended dose of azathioprine is 2–2.5 mg/kg/day and 6MP is 1.0–1.5 mg/kg/day.

1. Thiopurine monotherapy should not be used for induction of remission in active Crohn's disease.
The slow onset of action of these drugs limits their use as induction therapy.[1,2]

2. The early introduction of maintenance therapy with thiopurines is recommended for patients requiring corticosteroids.
Thiopurines are effective in the maintenance of CD and offer steroid sparing effects over the long term.[1,2,42,43]

3. Thiopurines may be indicated in combination with biologics in order to reduce antibody formation.
Data from the SONIC study showed that the combination of azathioprine with infliximab is better than monotherapy with either agent.[44] This is largely due to reduced anti-drug antibody formation.[1,2,44] Combination therapy appears to be less important with adalimumab, likely due to lower immunogenicity.[45]

4. There is a high risk of relapse following the discontinuation of thiopurines and this should be born in mind.
A recent systematic review summarised the published data on thiopurine withdrawal in patients in clinical remission.[46] The relapse rate at 12 months ranged from 16.5% to 53%.[46] Long-term data are scanty, with relapse rates at 5 years ranging from 63% to 85%. Fortunately, most patients will regain control of the disease on reintroduction of thiopurines.

2.2 Methotrexate
1. Methotrexate monotherapy should not be used for the induction of remission in Crohn's disease.
The slow onset of action of these drugs limits the use of MTX as induction therapy.[1,2]

2. Methotrexate is recommended for the maintenance of remission in Crohn's disease.
There is good data from both a Cochrane review and a large randomised controlled trial to support the role of MTX in the maintenance of remission.[47,48] Subcutaneous or intra-muscular administration has been proven to offer better bioavailability than oral methotrexate and wherever possible patients should administer MTX subcutaneously.[1,2] Concurrent therapy of folic acid should be prescribed.

3. Methotrexate may be used in combination with biologics to reduce immunogenicity.
Data from the recently published UK Personalised Anti-TNF therapy in CD study (PANTs) study showed that combination of an anti-TNF biologic with an immunomodulator significantly reduced the formation of anti-drug antibodies.[49]

Anti - TNF drugs in IBD
Infliximab, adalimumab, and golimumab are monoclonal antibodies directed against tumour necrosis factor alpha (TNF-α). They have been shown to be highly effective in IBD.1-6 In South Africa, infliximab (IFX) and adalimumab are approved for both UC and CD, while golimumab is only approved for UC.

The recommended dosing for infliximab is 5 mg/kg at week 0, 2, 6, and then every 8 weeks.

The recommended dosing for adalimumab is 160 mg SC at week 0, 80 mg SC at week 2, and 40 mg every other week thereafter.

The recommended dosing for golimumab is 200 mg SC at week 0, followed by 100 mg at week 2, and then 50–100 mg every 4 weeks.

Anti-TNF agents in Crohn's disease
1. Patients with active Crohn's disease either refractory or intolerant to conventional therapy (corticosteroid and immunomodulators, or either alone) can be treated with infliximab or adalimumab.[1-3]
In the seminal ACCENT I study infliximab was shown to be significantly more effective than placebo in inducing and maintain clinical remission in luminal CD.[50] Real world data support these results and suggests an even better response and remission rates than were reported in ACCENT I study.[51]

In the CLASSIC I induction study of moderate to severe CD naïve to anti-TNF therapy, clinical remission was achieved in 36% of patients receiving 160 mg/80 mg adalimumab induction therapy.[52] In the CHARM maintenance study significantly more adalimumab responders were in clinical remission at week 56.[53] The GAIN trial showed efficacy of adalimumab in patients with active CD and secondary loss of response or intolerance to infliximab.[54]

2. Rapid escalation of therapy should be considered in patients with severe Crohn's disease likely to have poor outcomes.
In patients with moderate to severe luminal CD, early use of anti-TNFs with or without immunomodulator therapy is indicated if there is a risk of a poor outcome, rather than gradual step-up after the failure of conventional therapies. Patients who are more likely to develop complicated CD include those with a younger age at diagnosis, smokers, a need for corticosteroids

at diagnosis, extensive disease, previous surgery, jejunal involvement and a stricturing or penetrating phenotype.[1-3]

3. Anti-TNF agents are considered equally efficacious in Crohn's disease. Choice of the agent must always consider the patient and physician preference.
Factors that may influence this choice include mode and frequency of administration as well as consideration of the relative need for combination therapy with an immunomodulator.1-3 Increased immunogenicity of infliximab may increase the need for co-prescription of an immunomodulator, which may impact safety.[49]

4. Patients should be maintained on the same anti-TNF agent which induced a clinical response.[1-3]
5. Patients in remission on a given anti-TNF agent should not be switched to a different anti-TNF formulation.
In the prospective randomised SWITCH trial, 47% of CD patients in remission on standard doses of infliximab who were switched to adalimumab 40 mg every other week either required dose escalation or were switched back to infliximab to maintain remission.[54]

6. The dose of the anti-TNF agent can be adjusted in patients with secondary loss of response or in primary non-response, when considered appropriate based on therapeutic drug monitoring.
For infliximab it is recommended to either reduce the dosing interval to 6 or 4 weekly or increase the dose to 10 mg/kg 8 weekly. Doubling the dose is generally more convenient and cost-effective than interval shortening.[55]

For adalimumab it is recommended to reduce the dosing interval to 40 mg SC weekly. The use of therapeutic drug monitoring (TDM) can guide whether dose intensification is appropriate (see section 6).

Combination therapy of an anti-TNF agent together with an immunomodulator in Crohn's disease
Combination therapy with an immunomodulator should be considered in order to maximise the benefits of anti-TNFs and reduce treatment failure, This strategy reduces immunogenicity and increases drug trough levels.[1-3] Evidence is strongest for the combination of infliximab and thiopurines.[45,49 53-56] Data supporting the combination of infliximab with methotrexate is less robust. Given reduced immunogenicity, adalimumab may be administered as monotherapy. In patients who are unable to receive combination therapy with an immunomodulator due to contraindications or intolerance, adalimumab is preferred over infliximab, unless other compelling reasons such as the presence of perianal disease prevail.[1]

Thiopurines should be avoided in patients over the age of 65 years unless other alternatives are not available.[1] Thiopurines should be used with caution in young males as combination therapy increases the risk of lymphoproliferative disease and hepatosplenic T cell lymphoma. Although controversial, similar precautions should be exercised in patients who test negative for Epstein Barr virus due to the risks associated with primary infection.

1. Whenever possible infliximab should be used in combination with a thiopurine for the induction and maintenance of remission in active Crohn's disease.
The SONIC study showed that the combination of infliximab and azathioprine was superior to either drug administered alone, in achieving clinical remission or mucosal healing.[44] This was confirmed in subsequent studies where combination therapy also appeared to reduce the need for infliximab dose escalation and reduced the rate of drug switching.[57] In the PANTS 3-year observational cohort of 1601 Crohn's patients treated with anti-TNF agents, combination therapy with an IMM reduced the risk of immunogenicity (HR=0.37, p<0.0001).[49] In patients treated with combination therapy, reduced formation of anti- drug antibodies most likely accounts for the improved response rates.

2. Combination therapy of infliximab with methotrexate therapy may be used in Crohn's disease to reduce immunogenicity.
Although the data supporting the use of methotrexate in combination with an anti-TNF agent is less robust, methotrexate is likely to reduce immunogenicity to infliximab and should be considered if thiopurines are ineffective or contraindicated.[1-3]

3. Combination therapy with an immunomodulator should be considered in patients receiving adalimumab in order to reduce immunogenicity and increase drug levels.
The value of combination therapy with an immunomodulator is not as clear in patients treated with adalimumab as it is for infliximab. The only randomised controlled trial to address this issue to date, the DIAMOND study, compared adalimumab monotherapy to combination therapy with azathioprine and showed similar remission rates at week 52.[45] Similar results have been reported in other studies. There is however good data showing that combination therapy is associated with higher trough levels and fewer anti-drug antibodies.[45,49] In addition, the DIAMOND study showed an improvement in endoscopic response at week 26 in patients receiving combination therapy.45 In the UK Personalised Anti-TNF therapy in CD study (PANTS), a 3-year observational cohort of Crohn's disease patients treated with anti-TNF agents, immunogenicity to adalimumab was present in 11% at 1 year and 23% at 3 years, and was associated with lower remission rates. Concomitant immunomodulator therapy reduced immunogenicity significantly (HR 0.34; 95% CI 0.21–0.56, p=0.0001).[49]

Anti-TNF's in ulcerative colitis

Induction of remission
1. Patients with active ulcerative colitis either refractory or intolerant to conventional therapy (5-ASA, corticosteroids, immunomodulators in combination or as monotherapy) may be treated with an anti-TNF agent (infliximab, adalimumab, or golimumab).[3-6]

2. Rapid escalation of therapy should be considered in patients with severe ulcerative colitis likely to have poor outcomes.
In patients with moderate to severe UC, including those patients who do not meet the criteria for acute severe UC, the early use of anti-TNF agents with or without an immunomodulator after the failure of conventional therapies, is preferable to a gradual step-up regimen particularly if there is a risk of a colectomy, Clinical predictors of the likely need for a colectomy in patients with UC include extensive disease, the need for corticosteroids, non-smoking status, and the need for hospitalisation.[6]

3. There is strong evidence supporting the use of infliximab, adalimumab, and golimumab in inducing remission in moderate to severe ulcerative colitis.
There are numerous randomised controlled trials

demonstrating the efficacy of anti-TNFs in inducing remission in moderate to severe UC. These include the registration trials: ACT 1 and ACT 2, which led to the registration of infliximab in 2005, the ULTRA 1 and ULTRA 2 trials for adalimumab, and the PURSUIT trials for golimumab.[58-62]

4. Infliximab appears to be the most effective anti-TNF agent inducing remission in patients with moderate to severe ulcerative colitis naïve to biologic therapy.
Although there have been no head-to-head trials comparing these agents, comparisons of the various anti-TNF agents based on network meta-analyses show superiority of infliximab over adalimumab (OR 2.10; 95% CI, 1.16–3.79).[63] Adalimumab or golimumb may be considered as first line therapy in patients where the convenience of self-administered subcutaneous dosing outweighs the potential therapeutic benefit of infliximab, or if monotherapy is deemed necessary.

5. In patients with moderate to severe ulcerative colitis infliximab should be used in combination with a thiopurine.
Combination therapy of infliximab with a thiopurine compared to infliximab monotherapy was evaluated in the UC-SUCCESS trial. Combination therapy was more effective at inducing a corticosteroid-free remission at week 16 compared with infliximab monotherapy (RR 1.78; 95% CI, 1.08–1.94).[38] Although there are no direct trials favouring combination therapy of adalimumab and a thiopurine, there is indirect evidence in patients with CD indicating that this combination reduces immunogenicity.[49] Although methotrexate has not been shown to effective in UC, low dose therapy may be of value in combination with an anti-TNF agent in order to reduce immunogenicity.

In patients with less severe disease, where there is concern regarding the adverse effects of an immunomodulator, the use of biologic monotherapy is a reasonable approach.

6. The anti-TNF agent used to induce remission should be continued to maintain remission.
There is a wealth of evidence supporting the efficacy of all three available anti-TNF agents in the maintenance of remission in patients with moderate to severe UC who have responded to induction therapy with that agent.[3-6]

7. In patients with moderate to severe ulcerative colitis who have achieved remission with anti-TNF agents with or without the addition of an immunomodulator, consideration should be given to stopping 5-ASA therapy.
Several large studies have demonstrated that discontinuing 5-ASA in patients with UC who commence anti-TNF therapy or vedolizumab did not increase the risk of adverse clinical events.[20, 21]

8. In patients on anti-TNF therapy who experience primary non-response or secondary loss of response, further management should be guided by the results of therapeutic drug monitoring.
Given the limited number of biologic agents available in SA and the cost of the newer classes of biologics, treatment with anti-TNFs should be optimised by measuring trough levels and anti-drug antibodies.[64]

Discontinuing anti-TNF biologic therapy in IBD
Structured de-escalation and discontinuing biologic therapy have only been studied in patients treated with infliximab and adalimumab. Presently there is a lack of data for exit strategies for all other biologic agents.

Biologic therapy has proven efficacy in moderate to severe CD and UC.[1-6] However, certain factors, such as cost, patient preference, infection and the risk of malignancy may prompt discontinuation of biologic therapy.[3,65-72] The decision to stop anti-TNF treatment in patients with primary non-response, secondary loss of response or severe side effects is straightforward. However, the decision to discontinue treatment in patients in remission is more difficult since the risk of disease relapse remains a concern. Studies assessing the outcome of discontinuing therapy after at least 12 months of anti-TNF treatment, indicate that the relapse rate at 1 year was 39% for CD and 35% for UC.[65] The estimated relapse rates at 2 years were 54% for CD and 42% for UC. Among patients relapsing that were retreated with an anti-TNF agent, approximately 80% will regain remission on retreatment.[65-72] The clinical factors associated with a higher risk of relapse on discontinuing an anti-TNF agent are still not clearly defined but younger age, smoking, a longer disease duration, the presence of perianal CD, anaemia, a raised CRP, a raised faecal calprotectin, escalated dosages of the anti-TNF agent in the past, and post-operative recurrence are all risk factors that are associated with a higher risk of relapse.[3,65-72] in contrast, mucosal healing and low serum drug levels are associated with a lower risk of relapse.[3,72]

1. Withdrawal of biologic therapy may be considered in highly selected patients who have achieved durable corticosteroid-free clinical, biochemical, and endoscopic remission.
The only group of patients that may be considered for discontinuation of therapy are those patients that are in deep, prolonged corticosteroid-free remission. Deep remission is characterized by clinical remission, intestinal mucosal healing, normal inflammatory markers, and low faecal calprotectin. The decisions to withdraw biologic therapy should be individualized and factors that need to be taking into consideration include the specific patient, the disease history, and the consequences of relapse.

2. Biologic withdrawal in certain high-risk patient populations is relatively contraindicated.
High risk patients include those with:
- Perianal CD.
- Active disease on endoscopy or on cross sectional imaging.
- Elevated inflammatory markers or elevated faecal calprotectin.
- Patients requiring biologic switching, dose escalation, or re-introduction in the past.
- Patients who have undergone surgical intervention.

3. Retreatment strategies after the withdrawal of a biologic should involve re-induction with the same agent.

Therapeutic drug monitoring of anti-TNF agents
One-third of patients treated with an anti-TNF agent will have a primary non-response while secondary loss of response during maintenance therapy occurs in roughly 20–40% of those who have an initial response.[73,76] Therapeutic Drug monitoring (TDM) is used to assist with the appropriate utilization of anti-TNF agents in these situations and is called reactive TDM. TDM can also be performed proactively in patients who are in remission. TDM entails the measurement of drug trough levels (TLs) and anti-drug antibodies (ADAs).

Three scenarios are encountered with TDM.[49,77,79]

1. Low TLS with no ADAs should prompt an increase of the dose of the anti-TNF agent or the dosing interval should be shortened.[49.77-79]
Increasing the drug levels of infliximab by doubling the dose to 10 mg/kg is generally more convenient and cost-effective than shortening the infusion interval to 6 weeks or even 4 weeks.55 For patients treated with adalimumab increasing the dose to 40mg weekly may suffice.

2. Low TLs with high levels of ADAs should prompt a switch to another anti-TNF agent.
It is unclear what antibody level is clinically meaningful. Low titer antibodies may be transient and non-neutralizing, and therefore shortening the dosing interval, escalating the dose, or adding an immunomodulator may suffice. In contrast, high titer ADAs, especially with undetectable trough concentrations, are generally persistent and neutralizing and therefore require a switch to another anti-TNF agent.[49,77,79]

3. Therapeutic or supra-therapeutic TLs should prompt a switch to another class of biologic.
In this situation the disease is not driven by TNF-α.[5-7]
Serum TLs and ADA of infliximab and adalimumab are routinely available in SA. Although vedolizumab assays are available, due to a paucity of data at this time, we have not addressed the role of TDM in patients treated with vedolizumab or ustekinumab.

4. In order to test TLs and ADA blood should be drawn as close to the next dose as possible and preferably within 24 hours. This is more important for infliximab than for adalimumab.

Reactive TDM
1. TDM can aid clinical decision-making in patients with primary non-response.
TDM can assist if primary non-response is driven by inadequate TLs, the rapid development of ADAs, or from anti-TNF refractory disease. TDM should be considered at the end of induction therapy in primary non-responders. Recent data from the UK Personalised Anti- TNF therapy in CD study (PANTS) revealed that the only factor independently associated with primary non-response was a low drug concentration at week 14.[49] Optimal week 14 drug concentrations associated with remission at both week 14 and week 54 were 7 mg/L for infliximab and 12 mg/L for adalimumab.

2. TDM should be performed in patients with secondary loss of response to guide clinical decision-making.
TDM may inform treatment strategies in patients with secondary loss of response. Results of TDM may aid in choosing dose intensification strategies, switching within a class, or switching out-of-class. While reactive TDM has not been shown to improve clinical outcomes it has been shown to be cost effective.[77] However, optimal target trough concentrations for achieving clinical, endoscopic and biochemical targets are uncertain and continue to evolve.[80-82] Higher TLs may be required to achieve mucosal healing than those suggested for achieving clinical remission, and higher trough levels may also be required for patients with perianal fistulising disease in order to achieve remission.[82]

Proactive TDM
The role of proactive TDM is more controversial than reactive TDM.

There is little consensus among recently published international guidelines which present contrasting recommendations. Proactive monitoring is not advocated by the American Gastroenterology Association (AGA)[77] but other associations consider it in order to optimise therapy.[78,79]

1. We concur with the Australian and BRIDGE guidelines that proactive TDM could be considered periodically in patients in clinical remission if the results are likely to impact management.[78,79]
As with reactive TDM optimal TLs are unclear.

Vedolizumab in IBD
Vedolizumab is a humanised monoclonal antibody targeting the α4β7 integrin, which is expressed on circulating B and T lymphocytes. It is gut specific, selectively blocking gut lymphocyte trafficking. It is given intravenously at a dose of 300 mg intravenously at 0, 2, and 6 weeks followed by 8 weekly infusions.

Vedolizumab has an excellent safety profile. A recent integrated safety review of six trials (2830 patients had 4811 patient years of vedolizumab exposure) failed to reveal an increased risk of any infection or serious infection associated with vedolizumab exposure.[83] Another recent post-marketing safety data review showed a low frequency of tuberculosis and there was no reactivation of hepatitis B/C viral infections.[84]

Induction of remission in ulcerative colitis
1. Vedolizumab is indicated in the induction of remission for patients with moderate to severe ulcerative colitis who have either failed anti-TNF therapy, are intolerant of anti-TNF therapy, or are who biologic naïve.
In the seminal GEMINI 1 study vedolizumab was shown to be more effective than placebo in inducing clinical remission and endoscopic improvement in patients with moderately to severely active UC.[85] Head-to-head comparison of vedolizumab and adalimumab in the VARSITY trial showed vedolizumab to be superior in achieving clinical remission (31.3% vs. 22.5%, p=0.006) and endoscopic improvement (39.7% vs. 27.7%, p<0.001).[86] Recent AGA guidelines support the use of vedolizumab as first line biologic therapy [87]
Vedolizumab is more effective in biologic naïve patients than patients previously exposed to anti-TNFs.[85]

2. The value of combination therapy with immunomodulators remains unclear. However, given the very low immunogenicity of vedolizumab, monotherapy is a consideration.

Maintenance of remission in ulcerative colitis
1. Vedolizumab is indicated for the maintenance of remission in patients with moderate to severe ulcerative colitis who have responded to this biologic.
Following induction of remission, vedolizumab may be continued in the maintenance of remission.[85] In the GEMINI 1 study, vedolizumab was shown to be more effective than placebo in maintaining clinical and endoscopic remission in severe ulcerative colitis.[85]

2. The value of combination therapy with an immunomodulator in the treatment of ulcerative colitis remains unclear. However, given the very low immunogenicity of vedolizumab, monotherapy is currently recommended.

3. Vedolizumab is not recommended for use in acute

severe ulcerative colitis (ASUC)
Vedolizumab should not be used to achieve remission in ASUC as it has not been evaluated prospectively in this setting. It is however recommended in maintaining remission following induction with cyclosporin.[88]

4. There is currently insufficient data to support the routine use of TDM in the management of IBD patients receiving vedolizumab.

Induction of remission in Crohn's disease
1. Vedolizumab is indicated as an induction agent for moderate to severe Crohn's disease who have either failed anti-TNF therapy, are intolerant of anti-TNF therapy, or who are biologic naïve.
In moderately to severely active CD vedolizumab may be used for induction of remission.[89,90] In the GEMINI 2 and 3 trials vedolizumab was shown to be superior to placebo.[89,90] Biologic naïve patients treated with vedolizumab have superior outcomes compared to patients previously exposed to an anti-TNF.[91,92]

2. Recent ECCO guidelines support the use of either ustekinumab or vedolizumab equally for the treatment of moderate-to-severe active luminal Crohn's disease in patients who have previously failed anti-TNF therapy.[2]

3.The value of combination therapy with immunomodulators in induction remains unclear. However, given the very low immunogenicity of vedolizumab, monotherapy is a consideration

Maintenance of remission in Crohn's disease
1. Vedolizumab is indicated for the maintenance of remission in patients with moderate to severe Crohn's disease who have responded to vedolizumab.
Vedolizumab has been shown to be effective in the maintenance of clinical remission in patients with CD. In the GEMINI 2 study, 39% of patients receiving vedolizumab every 8 weeks and 36.4% receiving vedolizumab every 4 weeks were in clinical remission at week 52 compared with 21% of those receiving placebo ($p<0.001$ and $p=0.004$ for the two vedolizumab groups, respectively, vs. placebo).Vedolizumab maintenance therapy provides persistent clinical benefit with long-term treatment regardless of prior anti-TNF exposure.[7-10] In general, however, biologic naïve patients have superior outcomes than patients who have been previously exposed to an anti-TNF.[89,91,92]

2. The value of combination therapy with immunomodulators in maintenance therapy remains unclear. However, given the very low immunogenicity of vedolizumab, monotherapy may be considered.

3. There is currently insufficient data to support the routine use of TDM in the management of IBD patients receiving vedolizumab.

The role of vedolizumab in fistulising disease is unclear.
Data from the GEMINI 2 study suggested an improvement in perianal fistulas in patients treated with vedolizumab. This study, however, was not powered to assess this endpoint.[94] A single, small randomised, double-blind phase 4 trial, the ENTERPRISE study (only presented in abstract form), evaluated the role of vedolizumab in fistulising CD. Vedolizumab was shown to be superior to placebo, with higher rates of fistula closure and fistulae that closed more rapidly.95 Clinically relevant reductions in draining fistulae were seen as early as week 2 and maintained through to week 30.[12] This study however was terminated earlier due to issues with recruitment and clearly more data is required before vedolizumab is recommended for fistulising CD.

Ustekinumab
Ustekinumab is a monoclonal antibody targeting the shared 40 sub-unit of interleukin-12 and interleukin-23. The main advantages of ustekinumab use are an excellent safety profile and very low rates of immunogenicity.[96]

Induction of remission in ulcerative colitis
1. Ustekinumab is indicated as an induction agent for patients with moderate to severe ulcerative colitis who have either failed anti-TNF therapy, are intolerant of anti-TNF therapy, or are who biologic naïve.
In the Phase 3 UNIFI program, ustekinumab was superior to placebo for inducing clinical response and remission, as well as endoscopic improvement.[97]

As expected, patients who were biologic naïve had higher rates of clinical remission, endoscopic improvement, and histologic improvement than the subgroup of patients who had previously failed treatment with biologic agents.[97] Recent AGA guidelines support the use of ustekinumab rather than adalimumab or vedolizumab in patients previously exposed to infliximab for inducing remission.[87]

2. The use of immunodulators in combination with ustekinumab in the treatment of ulcerative colitis has not been investigated in randomised controlled trials.
The UNIFI trial design did not address the issue of concurrent immunomodulator therapy and therefore the use of ustekinumab in combination with an immunomodulator is unclear.

Maintenance of remission in ulcerative colitis
1. Ustekinumab is indicated for the maintenance of remission in patients with moderate to severe ulcerative colitis who have responded to this biologic agent.
In the maintenance phase of the UNIFI study remission rates of 38.4% and 43.8% were seen for the 130 mg and the 6 mg/kg ustekinumab arms. Although not statistically significant, there was a slight superiority of the 8 week versus the 12 week regimen.[97]

2. There is currently no data to support TDM with drug levels or antibodies in the management of ulcerative colitis patients receiving ustekinumab.

Induction of remission in Crohn's disease
1. Ustekinumab is indicated as an induction agent for patients with moderate to severe Crohn's disease who have either failed anti-TNF therapy, are intolerant to anti-TNF therapy, or who are biologic naïve.
Ustekinumab was shown to be superior to placebo for inducing clinical response and remission, as well as endoscopic and histologic improvement in the Phase 3 UNITI program.[98]

As expected, patients who were biologic naïve had higher rates of clinical remission, endoscopic improvement, and histologic improvement than the subgroup of patients who had previous treatment failure with biologic agents.

2. Recent ECCO guidelines support the use of either ustekinumab or vedolizumab equally for the treatment

of moderate to severe active luminal Crohn's disease in patients who have previously failed anti-TNF therapy.[2]

3. The value of combination therapy with immunomodulators in induction remains unclear. However, given the very low immunogenicity of ustekinumab, monotherapy may be considered.

Maintenance of remission in Crohn's disease

1. Ustekinumab is indicated for maintenance of remission in patients with moderate to severe Crohn's disease who have responded to ustekinumab.

In the IM-UNITI maintenance trial, subcutaneous ustekinumab maintained remission in patients who had a clinical response to induction therapy; the percentage of patients who were in remission at week 44 was significantly higher in the groups that received 90 mg of ustekinumab every 8 weeks or every 12 weeks (53.1% and 48.8%, respectively) than in the placebo group (35.9%), with an absolute difference between treatment every 8 weeks and placebo of 17.2% (95% CI, 5.3–29.2, p=0.005) and between treatment every 12 weeks and placebo of 13% (95% CI, 1.1–24.9, p=0.04).98 Real world data also support the efficacy of ustekinumab in maintaining remission in a high proportion of patients with CD who are resistant to a conventional immunosuppressant and an anti-TNF agent.[99,100]

Long term data are now available showing that continued treatment with subcutaneous ustekinumab maintained clinical response and remission through 3 years in most patients who responded to induction therapy and was well tolerated.[101]

2. The value of combination therapy with ustekinumab and an immunomodulator in maintenance therapy remains unclear. However, given the very low immunogenicity of ustekinumab, monotherapy is a consideration.

3. The role of ustekinumab in the management of fistulising and/or peri-anal disease is unclear as there is insufficient data.

Although there is some data suggesting that ustekinumab may be beneficial in fistulising CD, there are no prospective randomised trials that have been published to evaluate this specific scenario.[102-103]

4. There is currently insufficient data to support TDM with drug levels or antibodies in the management Crohn's disease patients receiving ustekinumab.

Acute severe ulcerative colitis (ASUC)

ASUC is a medical emergency as it carries the risk of toxic megacolon and perforation.

1. All patients with ASUC should be admitted and managed by a multi-disciplinary team.

ASUC is associated with a considerable risk of failed medical therapy and subsequent colectomy. As such, all patients with ASUC should be managed by a team including a stomatherapist and a colorectal surgeon.[3]

2. All patients should have an infectious disease work up on admission, including a stool sample to exclude *C difficile* infection and a flexible sigmoidoscopy with colon biopsies to exclude cytomegalovirus (CMV) infection.

C. difficile infection has been associated with a worse outcome in hospitalised ASUC.[104,105] If *C. difficile* is detected treatment with oral vancomycin should be initiated.[3]

CMV is often present in the inflamed colon and in the setting of UC may render the disease refractory to corticosteroid therapy. On admission, flexible sigmoidoscopy is recommended to confirm the diagnosis of UC and obtain histology for CMV infection. If CMV is identified this infection should be treated in addition to therapies targeting the active UC disease.[106,107]

3. All patients should receive prophylaxis for venous thromboembolic disease.

Patients with IBD, especially those with active disease, are at high risk of VTE.[108,109] All patients admitted with ASUC should receive prophylactic subcutaneous low molecular weight heparin. This strategy does not appear to increase the risk of bleeding.

3. Intravenous corticosteroids are first line treatment for ASUC.

Once a flare has been confirmed, intravenous corticosteroids should be commenced as soon as possible, at doses equivalent to hydrocortisone 100 mg four times daily. It is not recommended to withhold steroids until stool or biopsy results are obtained. Approximately two thirds of patients with ASUC will achieve rapid control with intravenous corticosteroids.[110] A systematic review of 1991 patients evaluating corticosteroid therapy for ASUC reported an overall response of 67%, with 29% failing corticosteroids and requiring colectomy.[110]

4. Patients should be assessed for a clinical and biochemical response after 3 days of intravenous steroid therapy to determine the response to corticosteroids.

It is essential to identify corticosteroid failures early after admission as there is a small opportunity to save the colon with salvage therapies. This is best done using a validated index such as the Oxford criteria.[111]

5. Patients who fail to respond or have an incomplete response to corticosteroid therapy are candidates for salvage medical therapy or colectomy.

Infliximab and cyclosporine are equally efficacious as medical rescue therapy and the choice between these agents will depend on the individual patient and the attending physician.

Data from several prospective trials demonstrate similar efficacy and safety for infliximab compared to cyclosporin in patients with ASUC who are corticosteroid refractory.[112,113] Although infliximab is usually given at doses of 5 mg/kg, the use of higher doses as induction therapy or the use of an accelerated infliximab induction regimen has been proposed in very ill patients with ASUC. Protein loss through a very inflamed gut wall into the mucosa leading to low serum infliximab levels and reduced efficacy supports the rationale for this therapy.[3] The dose and duration of infliximab therapy is at the discretion of the attending clinician.

There is insufficient data to recommend other available medical therapies or biologics for the treatment of ASUC.

6. Extending medical therapy beyond 7-10 days carries no additional benefit and increases side effects; patient who have not responded to medical therapy by 10 days or those with complications at any stage (such as toxic megacolon, severe haemorrhage or perforation) should be referred for colectomy.

Prolonged admission prior to surgery is a significant predictor of post-operative complications as well as mortality.[114,115] Colectomy therefore should not be delayed in patients failing

medical therapy.

The management of perianal fistulizing Crohn's disease

1. Mesalamine and corticosteroids are ineffective treatments for fistulizing Crohn's disease.[1-3]

2. Antibiotics are indicated for the treatment of sepsis and may reduce fistula drainage. Antibiotics are not effective in long term fistula healing.

Antibiotics are widely used in the treatment of perianal CD despite the fact that most published studies are uncontrolled. Despite the lack of evidence to support their role as monotherapy in closing perianal fistulae, antibiotics are recommended to treat and control perianal sepsis.[2]

3. Infliximab is the preferred first-line medical therapy for complex perianal fistulae.[1-3]

In the seminal ACCENT II trial, fistula closure was seen in 69% of patients at 14 weeks. At 54 weeks 36% of infliximab-treated patients had a complete absence of draining fistulae compared with 19% of placebo patients (p=0.009).[116] Higher infliximab doses may be associated with better outcomes in patients with perianal fistulising disease and target levels of infliximab >10 µg/mL are associated with a better response.[82]

4. Adalimumab is effective in treating perianal fistulae but has never been assessed in a randomised controlled trial designed to test this endpoint.

Fistula closure or improvement has not been the primary outcome of any prospective randomised trials of adalimumab therapy. The CHARM trial revealed increased efficacy of adalimumab compared with placebo for the closure of abdominal or perianal fistulae as a secondary endpoint. Complete fistula closure at week 56 was seen in 33% of subjects on adalimumab versus 13% on placebo (p=0.016).[117] Of all the randomised patients in both arms, 90% of those with healed fistulae at week 56, maintained healing after a year of open-label adalimumab.[118]

5. Anti-TNF therapy should be withheld until any perianal sepsis has been treated.[1-3]

6. Combined surgical treatment with anti-TNF therapy appears to improve outcomes.

Several retrospective studies and a systematic review suggest improved outcomes with combined surgical and anti-TNF treatment, especially placement of setons followed by infliximab therapy.[119,120]

7. The efficacy of thiopurine monotherapy in treating perianal fistulae is limited. The main advantage of thiopurine therapy is to reduce immunogenicity in patients treated with anti-TNF therapy.

A meta-analysis on a limited group of patients demonstrated that azathioprine is not superior to placebo for fistula healing (RR, 2.00; 95% CI, 0.67–5.93). There is however evidence in luminal CD of reduced immunogenicity in patients receiving combination therapy with anti-TNFs and immunomodulators.[121]

8. There is insufficient to support the efficacy of vedolizumab or ustekinumab for fistula healing.

A post hoc analysis of 57 patients with fistulae (site not specified) treated with vedolizumab in the GEMINI 2 study showed a higher rate of closure of draining fistulae at 1 year compared to placebo (p=0.03 vs. placebo).[122]

Data for the outcomes of those patients with fistulae at baseline treated with ustekinumab in the CERTIFI phase 2 and UNITI phase 3 studies, have been reported in abstract form, showing a non-significant trend towards improved fistula healing in patients randomised to ustekinumab compared with placebo.[123] Further controlled trial data are needed to confirm the role of ustekinumab or vedolizumab in perianal fistula healing. However, ustekinumab or vedolizumab may be considered in patients where anti-TNFs are ineffective or contraindicated and there are no treatment options, especially when concomitant luminal disease is present.[2]

Positioning biological therapies

With burgeoning new therapeutic options for the treatment of IBD it has become important to position our therapies in the various treatment algorithms. The VARSITY study is the only published head to head trial of biologics in the field of IBD. This trial showed vedolizumab to be superior in achieving clinical remission and endoscopic improvement in patients with ulcerative colitis when compared to adalimumab (31.3% vs. 22.5%, p=0.006 and 39.7% vs. 27.7%, p<0.001 respectively).[86] Many more such studies are currently underway and until these are published, we need to rely on indirect comparisons from systematic reviews and network meta-analyses.

For the first time, recent guidelines are making recommendations on positioning biologic therapies in terms of efficacy, and as more data emerge these will likely evolve. Besides efficacy when choosing therapies, treatment safety profiles is a vital factor for both patients and physicians. And in this regard vedolizumab and ustekinumab have very favourable safety profiles.

Positioning biologics in Crohn's disease

Recent British Society of gastroenterology (BSG), European Crohn's and Colitis Organisation (ECCO), and American College of Gastroenterology (ACG) guidelines on the management of Crohn's disease make the following recommendations.1-3

1. Infliximab, adalimumab, ustekinumab, and vedolizumab are all appropriate as first line therapy in inducing remission in patients with moderate to severe active Crohn's disease who are biologic naïve.[1-3]

2. Ustekinumab, and vedolizumab are both indicated as second line therapy in patients with moderate to severely active Crohn's disease who have been exposed to anti-TNFs. ECCO recommends both ustekinumab and vedolizumab equally.[2]

Two systematic reviews and meta-analyses performed indirect comparisons of ustekinumab and vedolizumab for induction of remission in patients with moderate-to-severely active luminal CD who were previously exposed to anti-TNFs.[124,125] There were no significant differences between vedolizumab and ustekinumab in induction and maintenance of remission in TNF refractory CD patients.

3. The biologic agent used to induce remission should be continued as maintenance therapy.[1-3]

Positioning biologics in ulcerative colitis

Recent BSG, ACG, and American Gastroenterology Association (AGA) guidelines on the management of ulcerative colitis make the following recommendations

1. Infliximab, adalimumab, golimumab, ustekinumab, and vedolizumab are all effective as first line therapy in biologic naïve patients with moderate to severely active ulcerative colitis.[4,5,87]

2. The AGA recommends infliximab and vedolizumab above adalimumab for the induction of remission in biologic naïve patients.[87]
The VARSITY study showed vedolizumab to be superior in achieving clinical remission and endoscopic improvement in patients with ulcerative colitis when compared to adalimumab.[86] In a recent network meta-analysis, infliximab was ranked highest of the available biologics for induction of clinical remission in biologic-naïve patients (OR vs placebo, 4.07; 95% CI, 2.67–6.21; SUCRA, 0.95) and endoscopic improvement (SUCRA, 0.95).[126]

3. In infliximab exposed patients the AGA recommends ustekinumab above adalimumab or vedolizumab for the induction of remission.[6]
In the VARSITY trial, 21% patients had received prior treatment with an anti-TNF. In these patients, there were no significant differences in rates of a clinical remission at week 52 (20.3% vs. 16.0%).[86] In a network meta-analysis in patients with prior exposure to TNF antagonists, ustekinumab (SUCRA, 0.87) was superior to vedolizumab (OR vs. ustekinumab, 5.99; 95% CI, 1.13–31.76) and adalimumab (OR vs. ustekinumab, 10.71; 95% CI, 2.01–57.20).[126]

4. The biologic agent used to induce remission should be continued as maintenance therapy.

5. The benefit of switching to vedolizumab or ustekinumab over infliximab, in patients with prior exposure to adalimumab or golimumab, is uncertain.[87]

Biosimilars in IBD
Currently, an infliximab biosimilar CT-P13 and an adalimumab biosimilar have both been approved in SA for use in IBD. Most of the evidence presented below refers to CT-P13.

1. Locally approved anti-TNF biosimilars are considered appropriate for all clinical indications for which the reference product is licensed.
To attain regulatory approval a biosimilar has to have sufficient similarity in molecular structure, biological activity, efficacy, safety and immunogenicity. There should be no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.[127]

2. All biologics and biosimilars should be prescribed by brand name and not by international non-proprietary name (INN).
Biosimilars should be clearly distinguishable from the reference product, as well as from other biosimilars. They should be easily identifiable for patients, doctors and pharmacists alike. The INN of a biosimilar is not different from the original product, which may result in confusion and compromise post-marketing monitoring and patient safety.[128]

3. In biologic-naïve patients a biosimilar is an appropriate choice in patients who are eligible for anti-TNF therapy.
A meta-analysis of 11 studies were a biosimilar was used reported response rates for induction and maintenance therapy comparable to those published for the infliximab reference product in CD (79 and 77%, respectively) and UC (74 and 77%, respectively).[129] In patients with CD the first head-to-head trial in anti-TNF-naïve patients has recently been published.[130] Clinical response rates were not significantly different at week 54 with similar safety and immunogenicity profiles for the infliximab reference product and for CT-P13. Data from a large Italian cohort study supports this finding.[131] Most recently a large, real-world cohort of 5050 infliximab-naïve patients with CD who received either the infliximab reference product or CT-P13 revealed no difference in clinical outcomes. There was no difference in the rates of serious infection, tuberculosis and solid or haematological cancers between the 2 groups of patients.[132]

5. Private health insurer, health administrator or regulator driven switches from reference product to a biosimilar of the same anti-TNF is not recommended without prior approval of the prescribing physician.

6. In patients with primary non-response, secondary loss of response or adverse events the anti-TNF reference product can be switched to a biosimilar of a different anti-TNF.

7. Patients with primary non-response, secondary loss of response, or adverse events due to immunogenicity, should not be treated with a biosimilar of the same anti-TNF as this will not circumvent the problem.
In patients with IBD, cross-immunogenicity of CT-P13 and the IFX reference product has been demonstrated in a series of in vitro studies.[135]

8. Multiple switches between different anti-TNF biosimilars is not currently recommended due to lack of evidence.
9. Dispensing pharmacists should not substitute the reference product with a biosimilar without the permission from of the prescribing physician.
Substitution is the practice of dispensing one medical product to another interchangeable product at the pharmacy. This policy is widely adopted for generic medication where pharmacists can substitute the original product at their discretion. It
is currently nor recommended for biologics.

10. Dosing, administration and TDM of anti-TNF biosimilars is similar to the reference product.
Dose and treatment intervals should be maintained when switching from a biologic to the respective biosimilar. Similar clinical efficacy is present following the switch to a biosimilar without the need for dose adjustments.[136] Laboratory tests developed to measure infliximab trough levels and to detect ADAs are equally sensitive for the biosimilar as for the reference product. In a recent publication, samples that tested positive for antibodies to an infliximab reference product were then retested using a CT-P13 or a SB2 bridging assay; all tested positive for infliximab antibodies resulting in 100% test agreement.[137]

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POSITION PAPER ON THE USE OF DRUG THERAPIES IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

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