

# 2019 Expert opinion on biological treatment use in inflammatory bowel disease management

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## SECTION 1

### Optimal use of conventional drugs in the treatment of ulcerative colitis

Treatment strategy in ulcerative colitis (UC) is based on disease severity, extent (proctitis, left colon involvement, and extensive disease), and pattern (frequent relapsing, course, response to previous treatment, disease side effects, and extraintestinal involvement). Age at the onset of the disease and disease duration are also important. Severe disease may require inpatient treatment, whereas mild and moderate diseases may be treated on an outpatient basis. In UC, disease remission is associated with the resolution of clinical symptoms (diarrhea and rectal bleeding) and mucosal healing (resolution of inflammation and ulceration in endoscopy).

### Treatment in mild or moderate ulcerative proctitis

First-line treatment of mild or moderate UC includes symptomatic remission induction with rectally administered 5-aminosalicylic acid (ASA) (mesalazine) 1 g daily. Foam or enema formulations of mesalazine (mesalamine) may be used; however, mesalazine suppositories show better rectal distribution and are better tolerated than the other formulations. Topical forms of mesalazine are more effective than topical steroids (1). Combination therapy of topical and systemic mesalazine is associated with higher rates of clinical, endoscopic, and histological remission than monotherapy (2). Mesalazine suppositories at a dose of 1 g daily may induce clinical remission within 2 weeks in 64% of patients with proctitis and induce endoscopic remission within 4 weeks in 84% of patients (3,4). Topical mesalazine is more effective than oral mesalazine in the treatment of proctitis (5). Combination

treatment may be used if required. Rectal mesalazine at a dose of >1 g/day does not provide additional benefits.

### Treatment in mild to moderate UC (of any extent)

Oral 5-ASA preparations at doses of 2-4.8 g daily are the first-line treatment to induce complete remission induction in UC of any extent other than proctitis. Compliance with daily doses of orally administered 5-ASA is important in the maintenance of disease control. Combination therapy with oral and rectal 5-ASA preparations is a more effective alternative first-line treatment for inducing complete remission. In placebo-controlled studies, the rates of clinical remission and endoscopic mucosal healing after 8 weeks of treatment with oral multi-matrix mesalazine were found to be 40% and 32%, respectively (6). The rates of clinical remission and endoscopic mucosal healing after 8 weeks of combination treatment with oral 5-ASA 4 g daily and topical 5-ASA 1 g daily were found to be better than those of oral treatment alone (7,8). Although 5-ASA is not more effective than sulfasalazine (SASP), its medication tolerance is better. SASP should be preferred in patients with Crohn's disease (CD) associated with arthropathy. Adherence to daily doses of oral 5-ASA therapy is important for disease control; however, long-term adherence to oral preparations is poor, and an adherence <80% increases the risk for exacerbations; it has been shown that adherence might not improve, even with once daily doses (9).

Novel multi-matrix system formulation of budesonide provides the release of the drug throughout the colon, and its safety and efficacy have been demonstrated in mild to moderate UC (10). When compared with placebo, budesonide MMX administered for >8 weeks at a dose of 9 mg was found to be significantly more efficient in

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inducing clinical and endoscopic remission. Budesonide MMX can be used instead of conventional steroid therapy in patients with mild to moderate UC who have been unresponsive to optimized treatment with steroid (11).

Oral corticosteroids (CSs) are the second-line treatment for inducing remission in mild to moderate refractory, active UC. Meta-analysis has demonstrated that conventional CSs are significantly more efficient in inducing remission than placebo (12). Although the optimal dose of systemic steroids has not been settled in UC, meta-analysis has failed to show any evidence of additional benefits of steroids at doses >60 mg daily. A consensus has been achieved on a dose range of 40-60 mg daily (13). The optimal initial dose of prednisolone has been determined as 40 mg. Adverse effects are more prevalent with higher doses; however, additional therapeutic benefit from higher doses is limited (14). Oral prednisolone is used in a tapering regimen for 8 weeks. It is recommended to taper 5 mg prednisolone/week. Prednisolone therapy for <3 weeks has been associated with frequent relapses (15).

#### **Maintenance of remission in UC (patients who have entered into remission with 5-ASA)**

The 2-month relapse rates were found to be 41% with oral mesalazine and 58% with placebo in studies on the maintenance of clinical and endoscopic remission in UC (16). As with the induction of remission, higher maintenance doses ( $\geq 2$  g daily) are more effective (17). Topical mesalazine administered  $\geq 3$  times weekly has been proven to be effective in maintaining clinical and endoscopic remission of distal colitis (18). Although long-term rectal treatment is effective, studies have demonstrated that treatment with oral preparations alone has been preferred in 80% of patients (19). However, combination treatment with oral and topical preparations are more efficient than either oral or rectal treatment alone in maintaining remission; therefore, combination treatment may be considered to avoid to switch immunomodulatory agents or biologics in these patients (18).

#### **Treatment in moderate to severe UC**

CSs are the first-line treatment for inducing remission in moderate to severe UC. In moderate UC, steroids are given for 1-2 weeks at a dose of 40-60 mg daily. Steroids are tapered every 5 days or week and discontinued at the end of 8 weeks of treatment. Methylprednisolone administered intravenously at a dose of 60 mg daily may be effective in the treatment of severe, active UC. Although higher doses are not more effective, lower doses are less effective. Intravenous (iv) push administration is as effective as IV infusions. Maximum response to iv steroids is obtained within 3 days. Prolonged treatment for >7-10 days has no additional effect on the outcome. IV cyclosporine (CsA) monotherapy is an alternative treatment option in patients who have developed serious side effects associated with steroids. CsA

given intravenously at a dose of 2-4 mg/kg daily has been found to be as effective as methylprednisolone administered at a dose of 40 mg daily (20). Every patient should receive adequate IV fluids and low molecular weight heparin for thromboprophylaxis. Electrolyte imbalances should be restored, and anemia should be treated.

CSs are not recommended for maintenance of remission. Azathioprine (AZA) is indicated for the maintenance of remission. In a meta-analysis, AZA has been proven to be more effective in preventing UC relapses than placebo (21). AZA is more effective than 5-ASA in maintaining clinical and endoscopic remission in steroid-dependent UC (22). The optimum dose of AZA is found to be 2 mg/kg. Steroid-free remission rates provided by AZA in steroid-dependent patients at months 12, 24, and 36 were found to be 55%, 52%, and 45%, respectively (23). In an observational study lasting for 30 years, overall remission rate was found to be 58%, whereas the rates were found to be 87.5% at month 6 and 62% at year 5 in 346 patients who were treated with AZA. However, therapeutic outcomes are also associated with how well the treatment is tolerated and relapses occur at an average of 18 months after the discontinuation of AZA treatment (24). In a recent retrospective study, the 3-year relapse rate was found to be 36% in patients in long-lasting remission. Extensive UC or active disease at discontinuation or short-term treatment with AZA has been found to be risk factors for relapse, in particular (25).

## **SECTION 2**

### **Optimal use of conventional drugs in the treatment of CD**

Treatment recommendations in CD are based on the location, severity of the disease, disease-related complications, and prognosis. Therapeutic approaches are personalized on the basis of symptomatic response to medical interventions and medication tolerance. Medical treatment of CD is usually divided into two parts, which are induction of remission and maintenance of remission. Other therapeutic targets include prevention of disease complications, such as strictures and fistulae. Disease activity, location, and behavior should be considered during disease management planning, and the management plan should always be discussed with the patients. Drugs used in the conventional treatment of CD include 5-ASA, CSs, and immunomodulatory agents.

### **5-ASA**

5-ASA drugs include SASP, mesalazine, olsalazine, and balsalazide. SASP and mesalazine are available in Turkey. Oral and topical (suppositories, enema, and foam) formulations of mesalazine are also available in Turkey.

### **Indications**

5-ASA is a topical anti-inflammatory agent that is effective in the colonic lumen. Although the use of 5-ASA is

well-established in the treatment of UC and justified by evidence-based criteria, its use in CD has not been established yet. Oral mesalazine has not been proven to be more effective than placebo in inducing remission and ensuring mucosal healing in active CD (26-28).

SASP is formulated as a combination of 5-ASA and sulfapyridine. 5-ASA is responsible for the anti-inflammatory effect of this drug, whereas sulfapyridine is the transporter of this drug, ensuring the release of the drug into the colon. SASP (at doses of 3-6 g daily) is effective in the treatment of mild to moderate colonic CD and/or in resolving symptoms associated with ileocolonic CD; however, SASP is not effective in the treatment of patients with isolated small bowel disease. SASP has not been proven to be more effective than placebo in inducing mucosal healing in patients with CD (26). Eudragit-coated mesalazine has been reported to be effective in ileocolic or colonic disease at a dose of 3.2 g daily (29). Ethylcellulose-coated mesalazine has been reported to be effective in ileitis, ileocolitis, and colitis at a dose of 4 g daily (30). As a result, mesalazine has become a popular treatment for mild disease with a limited toxicity. However, systemic analyses of clinical study data and meta-analyses have failed to show any clinically significant improvement with ASA preparations versus placebo.

Based on the data reported to date, 5-ASA is not recommended in maintaining drug-induced remission (31).

#### **Clinical practice recommendations**

Based on the available evidence, both experts and consensus-based guidelines recommend the use of high-dose SASP (3-6 g daily) in CD, only in patients with limited disease. SASP should be used short-term, whereas active disease beyond 16 weeks of treatment should be considered as treatment failure. SASP is ineffective as maintenance treatment following drug-/surgery-induced remission (mesalazine may have a limited role in the latter). Furthermore, SASP may play a role in the management of patients with arthropathy associated with CD. However, a recent review of the available evidence indicated that benefit from SASP is limited to certain patients with peripheral arthropathy and early ankylosing spondylitis (i.e., patients with higher erythrocyte sedimentation rate (ESR) or active disease).

#### **Contraindications**

- History of drug hypersensitivity or any side effects associated with the drug
- Kidney impairment

#### **Side effects of ASA preparations**

Side effects associated with SASP may be seen in 10%-45% of patients in a dose-dependent manner, but se-

rious idiosyncratic reactions may occur (32). Mesalazine intolerance is very rare, and serious side effects are rare (33) (Table 1).

#### **Monitoring**

Although side effects are quite rare, a 6-month monitoring including complete blood count (CBC), urinalysis, liver tests, and kidney function tests (urea and creatinine) is recommended. The frequency and parameters of monitoring may be personalized according to comorbidities and concurrent medications.

The use of ASA in pregnant and breastfeeding women has been reported to be safe based on the IBHD and ECCO guidelines (34,35).

#### **Corticosteroids**

##### **Indications**

CSs (prednisone and methylprednisolone) are primarily used in active CD. Conventional CSs are effective in easing sign and symptoms and inducing remission in moderate to severe CD.

Steroids (e.g., hydrocortisone and 6-methylprednisolone) may be used intravenously in patients with more severe disease or in those who present with more severe acute manifestations; the superiority of IV administration over the oral route has not been proven. The main advantage of the IV route is to allow the administration of the drug in patients not tolerating oral intake.

Conventional CSs are not effective in providing mucosal healing. These may act as a "bridge" in providing symptom control and clinical remission in active disease until the onset of action of immunomodulatory agents.

Systemic CSs are ineffective as maintenance treatment of CD.

Controlled, ileal-release budesonide can provide short-term relief from mild to moderate CD symptoms in patients with disease limited to the ileum and right colon, although *budesonide* is not as effective as oral CSs, such as prednisone. Budesonide is a pH-dependent, ileal-release oral CS with high topical activity and low systemic bioavailability (~10%-20%). It has been proven to be effective in the treatment of mild to moderate ileocecal CD in randomized, placebo-controlled studies (34,35). It should be preferred over prednisolone when the extent and activity of the disease are appropriate for treatment with budesonide (36,37).

CSs play a role in the development of perforating complications (abscess and fistulas) and are contraindicated in patients who exhibit such symptoms.

**Table 1.** Side effects associated with sulfasalazine and aminosalicic acid.

	Common (>10%)	Rare (1%-10%)	Very rare (<1%)
Sulfasalazine	Nausea	Abdominal pain	Hepatitis
	Male infertility	Hemolytic anemia	Pneumonia
	Headache	Leukopenia	Neutropenia
	Rash	Thrombocytopenia	Pancreatitis Agranulocytosis
Aminosalicic acid	Watery diarrhea	Pancreatitis	Pneumonia
	Abdominal pain	Activation of colitis	Pericarditis
	Headache	Fever	Nephritis
	Nausea	Rash	Thrombocytopenia

**Dosage**

The initial dose of prednisone is 40 mg daily, and most patients respond to prednisone at this dose. In the treatment of active CD, the starting dose of prednisone varies from 40 to 60 mg daily, and the starting dose of methylprednisolone varies from 32 to 48 mg daily. These doses are maintained for 2-3 weeks at least, and the dose is tapered 5 mg/week until the weekly dose is reduced to 20 mg and then the dose is tapered 2.5-5.0 mg/week. This period should not exceed 3 months. Oral prednisone or other oral steroid formulation doses >60 mg are not recommended. There are limited comparative studies on different steroid-tapering regimens in the treatment of CD. However, it is recommended to taper off CSs upon discontinuation.

The risk for side effects associated with budesonide can be lowered by limiting treatment duration to 24 weeks and tapering off budesonide upon discontinuation after the first 3 months. The initial dose is 9 mg. The dose should be reduced to 6 mg after the first 3 months and discontinued within 6 months of treatment at most. Longer treatment durations have no effect on maintaining remission (12).

**Contraindications**

Contraindications include systemic fungal infections, herpes simplex keratitis, varicella infections, other uncontrolled systemic infections, and uncontrolled diabetes mellitus. The benefit-harm balance should be taken into consideration in patients with osteoporosis and in those who have a history of osteoporotic fractures.

**Side effects**

Three types of side effects can be defined. Although less severe than those associated with prednisolone in intensity, steroid side effects may occur with budesonide with similar

or lower frequency. *Immediate side effects* associated with supraphysiological doses used to induce remission in active CD include cosmetic effects (acne, moon face, edema, and striae), sleep and mood disorders, dyspepsia, and glucose intolerance. *Side effects associated with prolonged use* (usually >12 weeks, but it may be <12 weeks) include posterior subcapsular cataract, osteoporosis, osteonecrosis of the femoral head, myopathy, and susceptibility to infections.

Budesonide is less likely to decrease bone mineral density than prednisolone (in a randomized study, the mean decrease in 272 patients >2 years was found to be -1.04% vs. 3.04%,  $p=0.0084$ ) (38).

*Withdrawal side effects* include acute adrenal insufficiency (due to abrupt discontinuation), pseudo-rheumatoid syndrome (myalgia, fatigue, and arthralgia associated with manifestations similar to the recurrence of CD), or increased intracranial pressure. Therefore, CSs should be carefully used in CD.

**Monitoring**

Any metabolic disorders including blood glucose levels should be monitored in patients receiving CSs. The risk for developing hypertension should be taken into consideration, and a salt-free diet should be recommended. Vitamin D and calcium prophylaxis are recommended to prevent osteoporosis for treatment durations >6 weeks.

IV glucocorticoid support is required before surgery as the adrenocortical axis may be suppressed in patients who use systemic steroids at doses >20 mg.

Live vaccines should not be administered to patients who have received 20 mg prednisolone or equivalent/day. Vaccination is considered safe 1 month after the discontinuation of the medication.



- CBC, liver function tests (LFTs), creatinine, Papanicolaou test
- TPMT (if accessible)
- Radiology
  - Chest X-ray

### **TP treatment—induction and maintenance**

- *Empirical dose strategy*
  - Initial dose: 50 mg AZA or 25 mg MP
  - Slow dose increase (every 2 weeks)—until achieving the dose calculated per body weight kg
  - Follow-up: CBC, LFTs every week during the first month and then every 2 weeks for 2-3 months
- *TPMT dosing strategy*
  - TPMT is started at doses appropriate for disease activity
  - Follow-up: CBC, LFTs every 2 weeks for 1-3 months
- *Maintenance*
  - Maintenance dose: AZA: 2.0-2.5 mg/kg daily, MP: 1-1.5 mg/kg daily
  - Follow-up: CBC, C-reactive protein (CRP), LFT—every 3 months during the treatment
  - Measurement of TP metabolites, if applicable (6-TGN, 6-MMPN)—to assess efficacy and toxicity (38,40)

#### *How long should treatment duration be?*

- Discontinuation of TP treatment may be considered when objective signs of inflammation disappear (42)
- High rates of relapse have been reported from studies on the discontinuation of the drug
- Discontinuation of the drug should be considered on a patient basis and discussed with the patient

#### *Which patients can stop taking the drug?*

- In patients who have taken the drug for at least 4 years, discontinuation may be considered after taking into account:
  - The age of the patient
  - Depth of remission (clinical, serological, endoscopic)
  - Comorbidities
  - Risk for malignancy and infections associated with long-term treatment
- Close monitoring is required in patients who discontinue the drug (40)

A number of clinical studies, meta-analyses, and consensus notes have suggested that the use of TPs is safe during pregnancy and breastfeeding. The rates of spontaneous abortion, prematurity, low birth weight, congenital abnormalities, and neonatal adverse outcomes observed in pregnant women on TP treatment were not higher than those in women with IBD who do not receive any medication or treated with other drugs. Guidelines report that it can be used during pregnancy or breastfeeding (34,35).

### **Methotrexate**

Methotrexate (MTX) may be used in a way similar to TP. In a controlled study, 141 steroid-dependent patients with active CD were randomized to receive either MTX intramuscular (im) injections at a dose of 25 mg weekly or placebo. Prednisolone was tapered (20 mg at baseline) simultaneously over 3 months. In the MTX group, more patients could be withdrawn from steroids compared with the placebo group (39% vs. 19%,  $p=0.025$ ) (43). The efficacy was confirmed in a review (44).

Same indications as TP are applicable for MTX. However, MTX is still reserved to patients with active or relapsing CD, non-responsive or intolerant to TPs, or anti-tumor necrosis factor (TNF) agents.

### **Dosage and follow-up**

In contrast to rheumatoid arthritis, doses <15 mg weekly are ineffective in active CD, and standard induction dose is 25 mg weekly. In CD, MTX should be initiated via im or subcutaneous routes. Simultaneous folic acid support is recommended.

CBCs and LFTs should be performed within 4 weeks after the initiation of the treatment and then with longer intervals. The same warnings as for the follow-up of TP treatment are applicable for the follow-up of MTX. Patients should remain on the follow-up of a specialist for long-term. The duration of treatment is predicted to exceed 1 year (42-44).

### **Before starting treatment**

- CBC, creatinine concentration, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, bilirubin levels
- Hepatitis B and C and HIV serology
- Pregnancy test
- Chest X-ray

### **Monitoring toxicity during treatment**

- CBC and creatinine concentration every week in the beginning and every 2-3 months after the discontinuation of the treatment.
- Serum ALT, AST, and albumin levels every 4-6 weeks

### **Liver biopsy**

- If more than half of regularly monitored AST levels are >2-folds of the upper limit of normal
- In case of a progressive increase in serum levels of liver enzyme activity

### **Indications of MTX discontinuation**

- Clinically significant liver disease
- Fibrosis or cirrhosis in the histological examination of liver biopsy sample

**Side effects**

Immediate MTX toxicity is primarily gastrointestinal (nausea, vomiting, and stomatitis) and may be limited by initiating folic acid at a dose of 5 mg 2 or 3 days after the administration of MTX.

Although leukopenia, hepatotoxicity, hypersensitivity pneumonia, and opportunistic infections have been reported, these are not common.

Major long-term concerns are kidney impairment, hepatotoxicity, and pneumonia.

MTX should not be used by both sexes within at least 6 months prior to conception. It is contraindicated during pregnancy, and pregnancy should be deferred until 6 months after the discontinuation of the treatment.

MTX is contraindicated if glomerular filtration rate is <50 mL/min.

**SECTION 3****To do's before biological therapies are initiated in patients with IBD**

Biological therapies have radically changed our approach to the management of IBD over the last two decades. Anti-TNF (infliximab, adalimumab, and certolizumab pegol) and anti-integrin (vedolizumab (VDZ)) molecules have been approved as second- or third-line treatment of IBD in Turkey. The use of biologics has a moderate effect on disease progress with an acceptable increase in the risk for side effects. Safety concerns include risks for infections, reactivation of latent infections (e.g., fungal infection and granulomatous infection), malignancies, and autoimmune and neurological side effects. The use of a routine checklist before starting biological therapy will decrease the potential risk for side effects.

**Counseling before therapy**

A detailed medical history and a comprehensive evaluation of the disease type and activity are keys for establishing therapeutic indications and contraindications (Table 2). A thorough discussion with patients about the potential benefits and risks of biological therapies is also very important prior to initiating IBD treatment. Concomitant use of steroids and immunomodulatory agents is common among patients with IBD who need biologics. Unfortunately, concomitant use of other immunosuppressive drugs increases the risk for side effects, such as infections, and physicians must be aware of current medications (45). It is also important to set realistic goals for therapeutic success and advise patients about the early signs (e.g., fever, persistent cough, pain, and rash) of side effects. Patients with IBD on biologics should be able to contact their physicians or nurs-

es whenever they feel that something is not normal about their health condition. A clear communication is essential. Before starting treatment, patients need to undergo a series of diagnostic tests and vaccinations to decrease the potential side effects (Table 2).

**Tuberculosis screening**

It is well known that anti-TNF therapy increases the risk for flare-ups in latent tuberculosis (TB) (46). TB prophylaxis with isoniazid dramatically reduces this risk. A history of latent or active TB infection in the patient or his/her family is of paramount importance. A thorough evaluation of the patient's TB status including chest X-ray and preferably IGRA (interferon (IFN)-c release assay), such as QuantiFERON or TB spot tests, must be performed. If chest X-ray shows images compatible with TB, the patient should be referred to a pulmonary specialist.

IGRA tests might not be available in all clinics. In that case, TST (PPD) tests could be used, but IGRA test is more sensitive and specific. TST may be false positive due to prior BCG (Bacillus Calmette-Guerin) vaccination, and almost all members of the Turkish population are BCG-vaccinated. A TST (PPD)  $\leq 5$  mm must be considered positive. If the IGRA test or TST test is positive, then prophylactic isoniazid must be started and continued for 9 months. If the result of IGRA test is indeterminate, a second test must be performed. If the second test is negative, biologic treatment can be started. However, if it is still indeterminate or positive, prophylactic treatment is recommended for 1 month prior to anti-TNF therapy (47). Only in case of emergency, both isoniazid and an anti-TNF agent can be started simultaneously. It is important to keep in mind that the concomitant use of steroids or other immunosuppressive drugs may lead to false negative results. Biologic treatments are associated with a risk for latent TB reactivation, but proper screening before initiating treatment and prophylaxis along with regular controls can decrease the risk effectively.

**Hepatitis B**

Hepatitis B reactivation might be associated with significant morbidity and mortality in patients receiving anti-TNF therapy. Hepatitis B virus status should be determined before starting biological therapy in patients with IBD. HbsAg, anti-HBs, and anti-HBc IgG must be checked. All patients who tested negative for anti-HBs ( $\geq 10$  U) should be vaccinated. It is important to remember that the rate of response to hepatitis B vaccination may be low among patients with IBD (48-49). This could be due to impaired immune response to infectious agents in these patients, malnutrition, and use of other immunosuppressive drugs (50). An accelerated vaccination protocol with hepatitis B vaccine in double doses at months 0, 1, and 2 has been shown to increase response rates (51). Patients who tested positive for HbsAg need prophylaxis with oral

**Table 2.** Checklist before starting biologics.**Medical history check**

- Tuberculosis or history of tuberculosis
- Cardiovascular disorders
- Previous malignancy
- Respiratory disorders
- Hepatic disorders
- Joint symptoms
- Neurological diseases and symptoms
- Hematologic disorders
- Diabetes mellitus
- HIV
- STDs

**Blood tests**

- CBC/CRP/ESR
- BUN, creatinine
- LFT
- Anti-HIV
- Ani-HAV total
- HbsAg
- Anti-HBs
- Anti-HBc Ig G
- Anti-HCV
- QuantiFERON/TB Gold or PPD
- Chest X-ray
- Abdominal imaging (USG or CT or MRI)

**Immunizations**

- Hepatitis A
- Hepatitis B
- Pneumococcal (every 5 years)
- Influenza (annual)
- HPV (9–26 years old, female)
- Tetanus and diphtheria (every 10 years)

**Others**

- Cancer screenings (according to age and sex)
- Pregnancy issues

nucleos(t)ide analogues regardless of their active viral status 1–3 weeks before anti-TNF treatment. Prophylactic treatment must be maintained for 12 months at least after the discontinuation of biologics (52). Patients who tested positive for anti-HBc/negative for HbsAg may also show reactivation during anti-TNF treatment, but it is less common. Guidelines do not recommend prophylaxis for these patients and advise monitoring of HBV DNA and LFT levels during treatment (47).

**Hepatitis C**

Fortunately, concurrent hepatitis C infection in patients with IBD is uncommon.

The use of anti-TNF agents appears to be relatively safe in patients with chronic hepatitis C infection. However, anti-HCV should be checked before initiating anti-TNF treatment. If anti-HCV is positive, HCV-RNA status should be addressed, and appropriate therapy should be started accordingly (47). If compensated liver disease is present, anti-TNF agents should be used with caution, and the benefit/risk ratio should be considered. Anti-TNF agents are contraindicated in decompensated cirrhosis due to the high risk of potentially fatal infections (53).

**HIV infection**

Although TNF increases viral replication in HIV infection, biologics may also increase the risk of infection as a result of impaired immune function due to HIV infection. Therefore, the use of biologics should be carefully considered on the basis of risks versus benefits, and patients should also be monitored very carefully during the treatment period (54).

**Malignancy**

Before starting anti-TNF treatment, every patient should undergo screening tests for cancer, appropriate to their age/gender according to the local guidelines. Although the risk for cutaneous malignant melanoma is increased 1.32-fold in those treated with anti-TNF agents, guidelines emphasize that there is not enough evidence that monotherapy with anti-TNF drugs increases the overall risk of malignancy in patients with IBD (55–56). However, regarding the risk of lymphoma, data are conflicting. In a meta-analysis, a 3-fold increased risk of NHL was found in patients who were exposed to an immunomodulatory agent previously, whereas data obtained from observational studies and registries did not show an increased risk in patients exposed to an anti-TNF agent alone. In addition, in recent reports, there was an increase in the rare hepatosplenic T cell lymphoma cases in young male patients with IBD treated with AZA in combination with an anti-TNF agent (57). It is important to keep in mind that the Turkish Health Ministry reimbursement policy permits only step up treatments in IBD. Therefore, most of our patients

have already been exposed to immunomodulatory agents, and close follow-up is essential. Patients with a history of cancer and requiring biologic therapies present another challenge to physicians who treat patients with IBD. If the patient has completed oncologic treatment within 2 years, 5-aminosalicylates, CSs, antibiotics, nutritional therapy, and surgery should form the foundation of IBD treatment if applicable. The administration of conventional IS or an anti-TNF agent should be decided on a case-by-case basis by the oncologist and the patient in patients with refractory IBD. MTX could be an alternative to TPs and anti-TNF drugs. However, if necessary, anti-TNF drugs could be used after explaining the risk and benefits to the patient, with close collaboration with the oncologist (58).

### **Immunization**

Immunization of patients with IBD before starting immunosuppressive treatments can prevent serious infectious complications and must be in the checklist of physicians treating IBD (Table 3). As a rule, live attenuated vaccines (measles, mumps, rubella, polio, yellow fever, varicella, BCG, and oral typhoid) must be strictly avoided in patients receiving immunosuppressive therapy. The varicella vaccine should be considered in patients with no history of chickenpox or shingles, no prior immunization but with a negative serology for VZV. Since varicella vaccine is a live vaccine, it should be avoided in patients receiving immunomodulatory treatment. Patients should receive varicella vaccine according to a two-dose vaccination schedule at least 4 weeks before starting immunosuppression.

It is well known that inactivated vaccines are safe in immunocompromised patients. Inactivated vaccines against influenza and pneumococcal infections are recommended annually. Intranasal influenza vaccine is contraindicated in immunocompromised individuals. Hepatitis A and B antibody status should be checked, and if the patient tested negative for anti-HBs or anti-HAV total, vaccines should be administered. HPV vaccination is also recommended to female patients aged between 9 and 26 years for the prevention of cervical cancer (47).

### **Anti-integrin therapy**

VDZ is a humanized, monoclonal IgG1 antibody that blocks the heterodimer  $\alpha 4\beta 7$  integrin and inhibits migration and leukocytes adhesion. In contrast to non-selective  $\alpha 4\beta 1$  integrin antibody natalizumab, anti- $\alpha 4\beta 7$  integrin antibody VDZ is gut specific. Probably this is the main reason for the good safety profile of VDZ established from clinical studies and real-life data (59). The mechanism of action of VDZ is not expected to increase the risk for malignancies, although longer term data are needed for a comprehensive assessment. Colombel et al. have evaluated the safety data from six trials (2830 patients had 4811 PYs of VDZ exposure) VDZ was not associated with

an increased risk for infections/serious infections. Serious clostridial infections, sepsis, and tuberculosis were reported infrequently ( $\leq 0.6\%$  of patients). Most importantly, no cases of progressive multifocal leukoencephalopathy were observed (60). VDZ is a foreign protein, and allergic reactions should be expected. Fortunately, infusion reactions have been reported in  $< 5\%$  of cases (61). The current Turkish Health Ministry regulation requires screening for tuberculosis and neurological consultation prior to VDZ treatment although neither the risk for TB infections nor progressive multifocal leukoencephalopathy prevalence was higher than placebo.

### **Details to consider before starting treatment with biological agents**

If the clinical condition of the patient that the treatment planned allows, it is wise to avoid starting anti-TNF and immunomodulatory treatments concomitantly. Because if serious adverse events occur, it will be impossible to determine which one of these two agents causes the events. Before starting treatment with biological agents, albumin levels of the patients must be evaluated as the clearance of these agents increases in case of hypoalbuminemia and leads to decrease at the efficiency of drugs (62).

## **SECTION 4**

### **When to start biologics in UC? And how to use them effectively?**

Currently, anti-TNF and anti-integrin agents are included in established treatment protocols for the management of patients with UC. The success of biologics is assessed on the basis of clinical response, clinical remission, mucosal healing, and histological recovery and colectomy rates. Studies on biologics that are used in the management of UC are summarized in Table 4.

### **The role of anti-TNF agents in the management of patients with UC**

The mechanism of the pathogenesis in UC is a reduction in Th1 responses and an increase in Th2 responses. However, Th2 response is atypical in nature, IL-13 expression has been observed in CD4+ T lymphocytes (70), while in-

**Table 3.** Contraindications to anti-TNF therapy.

- |                                                                              |
|------------------------------------------------------------------------------|
| • Active infections                                                          |
| • Moderate-to-severe heart failure                                           |
| • Neurological demyelinating disorder                                        |
| • Optic neuritis                                                             |
| • Recent malignancy or previously treated malignancy within the last 5 years |
| • Congenital or acquired immunodeficiency                                    |

creased IL-1 $\beta$ , IL-4, IL-5, IL-8, IFN- $\gamma$  and TNF- $\alpha$  levels have been detected. Increased TNF- $\alpha$  levels have been also observed in mucosal and fecal samples. The efficacy of anti-TNF agents in patients with UC is based on this fact (71).

Infliximab (IFX), adalimumab (ADA), and golimumab (GM) have been approved for the treatment of UC. In well-designed, multicenter, randomized, controlled studies, anti-TNF agents have been proven to be superior over placebo in a number of parameters including clinical response, clinical remission, steroid-free remission, and mucosal healing in patients with moderate to severe UC unresponsive to conventional agents (64-69).

### **Induction of remission**

- Anti-TNF agents are indicated as the second-line treatment for inducing remission in UC, in patients with moderate to severe UC refractory or intolerant to oral CSs and/or immunomodulatory agents or if steroids are contraindicated, and in steroid-dependent patients if steroid-free remission cannot be achieved with immunomodulatory (IM) agents (72-76).
- As there are no studies comparing anti-TNF agents against one another, it has been suggested that these agents exhibit approximately equal efficacy based on placebo-controlled studies and meta-analyses.
- Anti-TNF agents may be used in combination with AZA/6-MP. The UC-SUCCESS study demonstrated that AZA given in addition to IFX prevented the development of ADAs, increased IFX "trough" levels and consequently, increased the efficacy of IFX (77).
- Anti-TNF agents may be used as a rescue treatment following 3 days of treatment with iv CSs in patients with acute severe UC (ASUC) and as an alternative to second-line cyclosporine therapy. They should be used in AZA-experienced patients who are on multidrug regimens, and when cyclosporine is contraindicated or not feasible (e.g., if serum levels cannot be measured) (72-74). Only IFX should be used as anti-TNF agent in patients with ASUC. The efficacy and colectomy rates associated with anti-TNF agents were higher or equal to those of cyclosporine (78,79).
- In the assessment of therapeutic efficacy, treatment should be reviewed in the absence of symptomatic response 8-10 weeks after anti-TNF loading (75). VDZ is an alternative biologic therapy to be used in cases of primary unresponsiveness.

### **Maintenance of remission**

- Remission is aimed to maintain steroid-free clinical and endoscopic improvement achieved in UC.
- Anti-TNF agents should be used in the maintenance of remission in patients who have responded to induction treatment with anti-TNF agents. Anti-TNF

agents may be used alone or in combination with AZA/6-MP to maintain remission (72,74).

- "Anti-drug antibodies" (ADAs) and drug levels should be measured in case of loss of efficacy during the maintenance therapy and alternative options, such as the use of anti-TNF agents at higher doses or the use of immunomodulatory agents should be considered.

### **Anti-integrin agents in the treatment of UC**

Currently, VDZ is the sole anti-integrin agent to be used in the treatment of UC. VDZ is a biologic agent that acts against  $\alpha 4\beta 7$  integrin and blocks the interactions of  $\alpha 4\beta 7$  integrin with "mucosal addressing cell adhesion molecule-1" on lymphocytes and endothelial surface, specifically in the gastrointestinal tract (80). In this way, VDZ inhibits inflammatory cell trafficking to the tissue.

### **Induction of remission**

- As with anti-TNF agents, VDZ is indicated in the second-line treatment for inducing remission in UC, in patients with moderate to severe UC, refractory or intolerant to oral CSs and/or IM therapy or in steroid-dependent patients or if steroids are contraindicated, and steroid-free remission cannot be achieved with IM agents or as an alternative biologic agent in case of primary or secondary loss of response to anti-TNF agents (73,75).
- VDZ is particularly more effective in anti-TNF-naive patients than in those who are anti-TNF experienced (69).
- The efficacy of combination therapy with VDZ and immunomodulatory agents has not been established (81).
- A definite period has not been specified for the assessment of the efficacy of the treatment. It is recommended to wait until week 16 of the treatment.
- VDZ is not indicated in patients with ASUC.

### **Maintenance of remission**

- Real-world data suggest that the efficacy of VDZ may increase cumulatively. VDZ may be used effectively in the maintenance of remission based on this observation (81).
- VDZ therapy should be continued until steroid-free remission is achieved in patients if induction therapy is successful.

### **Anti-TNF agents or anti-integrin agents?**

- Recently, it has been found in a randomized trial which was the first head to head trial comparing two biologic treatment (VDZ vs. adalimumab) in patients with active moderate to severe UC that VDZ showed superior efficacy over adalimumab in achieving clinical remission and mucosal healing at week 52. However, there was no significant difference in steroid-free remission between these two drug regimens (82).

**Table 4.** The efficacy of biologics versus placebo in patients with ulcerative colitis (adapted from reference (63)).

Study	Anti-TNF	Inflammatory Activity Treatment experience	Treatment phase	Doses	Clinical response* (%)	Clinical remission** (%)	Steroid-free remission (%)	Mucosal healing*** (%)	Colectomy (%)
ACT1 (63)	IFX	Mayo score $\geq 6$ , endoscopic subscore $\geq 2$ KS+AZA/6-MP	Induction/maintenance	5 mg/kg Weeks 0, 2, and 6 Every 8 weeks, iv	5 mg/kg, 10 mg/kg, placebo Week 8 (69.4 vs. 61 vs. 37.2) Week 54 (45.5 vs. 44 vs. 19.8)	Week 8 (38.3 vs. 14.9) Week 54 (34.7 vs. 16.5)	Week 30 (21.5 vs. 7.2)	Week 8 (62 vs. 33.9) Week 54 (45.5 vs. 18.2)	Week 54 (10 vs. 17)
ACT2 (64)	IFX	Mayo score $\geq 6$ , endoscopic subscore $\geq 2$ KS+AZA/6-MP+5-ASA	Induction/maintenance	5 mg/kg Weeks 0, 2, and 6 Every 8 weeks, iv	5 mg/kg, 10 mg/kg, placebo Week 8 (64.5 vs. 29.3) Week 54 (47.1 vs. 26)	Week 8 (33.9 vs. 5.7) Week 54 (25.6 vs. 10.6)		Week 8 (60.3 vs. 30.9) Week 30 (47.1 vs. 46.31)	
ULTRA-1 (65)	ADA	Mayo score $\geq 6$ , endoscopic subscore $\geq 2$ KS+AZA/6-MP	Induction	160/80/40 Every 2 weeks, SC	Week 8 (54.6 vs. 44.6)	Week 8 (18.5 vs. 10)	Week 16 (31 vs. 16)	Week 8 (46.9 vs. 41.5)	
ULTRA-2 (66)	ADA	Mayo score $\geq 6$ , endoscopic subscore $\geq 2$ KS+AZA/6-MP	Maintenance	160/80/40 Every 2 weeks, SC	Week 8 (50.4 vs. 34.6) Week 52 (30.2 vs. 18.3)	Week 8 (16.5 vs. 9.3) Week 52 (17.3 vs. 8.5)	Week 52 (13.3 vs. 5.7)	Week 8 (50.4 vs. 34.6) Week 52 (30.2 vs. 18.3)	Week 16 (31 vs. 16) Week 52 (13.3 vs. 5.7)
PURSUIT-SC (67)	GLM	Mayo score 6-12 Endoscopic subscore $>2$	Induction	Weeks 0 and 2 200 and 100 mg SC Every 2 weeks, 50-100 mg SC	Week 6 (51 vs. 30.3)	Week 6 (17.8 vs. 6.4)	Week 54 (34.4 vs. 20.7)	Week 6 (17.8 vs. 6.4)	
PURSUIT-M (68)	GLM	Patients responsive to GLM induction treatment	Induction/maintenance		Week 54 (49.7 vs. 31.2)	Week 54 (27.8 vs. 15.6)		Week 54 (42.4 vs. 26.6)	Week 54 (34.4 vs. 20.7) *
GEMINI-1 (69)	VDZ	Mayo score 6-12 endoscopic subscore $\geq 2$	Induction/maintenance	Loading dose of 300 mg iv Weeks 0 and 2 Every 4 and 8 weeks	Week 6 (47.1 vs. 25.5)	Week 52 (44.8 vs. 15.9)	Week 52 (45.2 vs. 13.9)	Week 6 (40.9 vs. 16.1)	

\*Clinical response;  $\geq 30\%$  or  $\geq$  points reduction from the baseline in Mayo scores, rectal bleeding subscore 0 or 1.

\*\*Clinical remission.

\*\*\*Mucosal healing; Mayo endoscopic subscore: 0.

- In patients with moderate to severe UC refractory to conventional treatment, anti-TNF agents are recommended in pregnant patients, in patients with ASUC, and in patients with extraintestinal manifestations, whereas anti-integrin agents are recommended in older patients, in patients with a history of serious, opportunistic infections, or in patients with extraintestinal cancers (83).
- VDZ is positioned as first-line biologic treatment, such as anti-TNF agents, in patients with moderate

to severe UC according to the recent guidelines published by the British Society of Gastroenterology and American College of Gastroenterology (84,85).

## SECTION 5

### **When to start biologics in CD? And how to use them effectively?**

Although the introduction of biologics, notably anti-TNF agents in the treatment of IBD, has strengthened clinicians' hand over the last 20 years, cure is not possible yet. Therefore, by switching to biologics before giving enough time to conventional treatment, a potentially appropriate treatment option would be prematurely excluded. Though slowly, increasing number of alternative treatments to biologics leads to confusion when deciding about which treatment is the treatment of choice under such conditions. Some of the important clinical studies on biological treatments are summarized in Table 5.

### **Role of anti-TNF agents in the treatment of CD**

In general, anti-TNFs are recommended in the treatment of moderate to severe CD after the failure of conventional treatments (31,86). However, the decision on conventional treatment failure still depends on personal perception, as the treatment duration and issues, such as the assessment of comorbidities and side effects, have not been clearly defined yet.

The basement of current biologic use has been extended by patients who are not having any alternative treatment option and suffer from chronic active disease in mild to moderate intensity in both endoscopic and clinic activities.

Anti-TNF agents can be used to induce remission in case of prior failure of remission induction therapy or if CSs are contraindicated. Anti-TNF treatment should be considered in patients who have become steroid-dependent or steroid refractory while receiving steroids or IM agents or if disease exacerbations cannot be kept under control. Switching from an IM therapy to another IM therapy or anti-TNF agents may be considered in patients intolerant to previous IM or who have developed side effects (31,87).

Management planning should be based on the assessment of disease activity and risk factors. There is no gold standard test or scoring scales to assess disease activity. Clinician's assessment based on clinical and endoscopic findings and data from medical history and examination of the patient is essential. Tests or scoring scales may provide the physician with only a partial objectivity.

Age <40 years at the time of diagnosis, ileal/ileocolic involvement, long-segment disease, and perianal involvement have been considered as risk factors for progressive

disease (88). It is well known that the combination of anti-TNF and IM has an additive effect in a patient who has not received these treatments before (89). Therefore, it appears to be rational to start with combination therapy including anti-TNF and IM agents to induce and maintain remission to prevent long-term complications in patients with multiple prognostic risk factors. Even though, which patients are more likely to benefit from long-term intensive treatment, it is a matter of debate (90,91).

We believe that anti-TNF agents and IM agents should be started with an interval of a few weeks, and CBCs and blood chemistry should be assessed before adding anti-TNF agents to IM therapy in patients considered for combination therapy, to avoid the dilemma of choosing which drug is the cause and subsequent discontinuation of both drugs.

- Anti-TNF agents are indicated in the treatment of moderate to severe CD after the failure of conventional treatments.
- Biologics may play a role in the treatment of chronic active, mild to moderate CD in patients who are non-responder to/unable to use IM agents.
- Combination treatment with TNF blockers and IM agents may be started in patients with risk factors for progressive disease.
- The components of combination therapy should be started separately with an interval of a few weeks.

### **Whether combination therapy (IM+anti-TNF) or monotherapy (anti-TNF) should be used when treatment with immunomodulatory agents fails?**

There are no studies demonstrating the extra benefits of adding anti-TNF agents to full-dose immunomodulatory agents in patients who failed to achieve clinical response/remission under IM therapy. Nevertheless, this approach does not provide any additional clinical benefits; several studies have suggested that this therapeutic approach might further increase the risk for opportunistic infections (92). On the other hand, it is well established that keeping low-dose IM in combination with anti-TNF agents reduces the immunogenicity of these biologics. Although anti-TNF agents are used as monotherapy by certain groups, it may be more rational to administer immunomodulatory therapy at lower doses to prevent anti-TNF antibodies from developing.

- There is no evidence of additional benefits of continuing IM therapy at full doses in patients who have switched to anti-TNF therapy after a treatment failure with IM agents.
- Combination with low-dose IM therapy with anti-TNF to prevent the development of antibodies may be more reasonable.

**Whether the dose should be increased when anti-TNF therapy fails? Whether to use another anti-TNF agent or switch to another therapy with a different mechanism of action?**

Primary non-response should be considered in case of non-response after the initiation of the therapy or a partial response which disappears within the first 3 months, whereas a secondary non-response should be considered if non-response occurs after 3 months of treatment. Primary non-response occurs in approximately one-third of patients who receive anti-TNF therapy, and secondary non-response occurs over time in approximately half of patients initially responsive to anti-TNF therapy (72). A second anti-TNF response is more common in patients intolerant to the first anti-TNF agent and least common among patients who exhibit primary non-response (93). In case of primary non-response, it is more rationale to switch to another group of biologics which are more likely to induce a response rather than trying another anti-TNF agent (94).

Dose increases are useless if the blood anti-TNF level is within therapeutic range (mechanistic loss of effect) for secondary non-responders to anti-TNF agents. There are studies investigating the success of a second anti-TNF agent in such cases (95,96). The recommendation is to switch to out of class biologics.

Patients who switched to adalimumab after developing antibodies against infliximab were found to be more likely to develop antibodies against this therapy too (97). In a study investigating secondary loss of response, the highest rate of patients who benefited from switching to a second anti-TNF agent after treatment failure with an anti-TNF agent was in the group of patients who had low drug levels. One can argue that this group of patients might also benefit from higher doses of the first anti-TNF agent (96). Low-dose MTX or AZA may be added to the regimen if a second anti-TNF agent will be given to a secondary non-responder due to neutralizing antibodies against the first anti-TNF agent. These patients may switch from anti-TNF therapy to another class of biologics.

Medical history and clinical assessment are of paramount importance in case of secondary loss of response, particularly when blood drug levels cannot be measured. If the patients are clinically doing well after receiving treatment but deteriorate just before the next dose, this means that this patient may benefit from dose intensification or escalation.

In case of loss of response in patients non-compliant with treatment, requiring frequent treatment interruptions or developing infusion reactions, the presence of antibodies is more likely.

If a sudden clinical deterioration occurs following an infection or acute abscess formation, this may suggest the

consumption of anti-TNF by infection-related TNF-alpha and consequent reduction in drug levels. In such patients, taking infectious process under control may provide clinical benefit by increasing the drug level. In a similar way, conditions associated with increased inflammatory load, such as infections, abscesses, or active sacroiliitis, drug level measurements may be misleading as these measurements are usually preplanned.

Regarding therapeutic drug level measurements, we have adopted a dynamic, reactive approach integrating medical history and clinical data of the patient and drug level measurements. Considering the conditions in our country, we believe that it is possible to manage the disease on the basis of clinical manifestations, medical history, and drug level measurements, when required, but putting the secondary importance to measuring antibody levels to lower healthcare costs.

- Switching to another biologic with different mechanism of action may be more appropriate in primary non-responders.
- Drug levels and clinical signs and symptoms may guide disease management in patients with loss of response.
- Presence of antibodies or mechanistic loss of effectiveness underlying as the cause of secondary non-response possibly suggests poor success rate in the same biologic group. The class of biologic agent may be changed in this group of patients.

**VDZ in the management of CD**

VDZ is a monoclonal antibody that acts against  $\alpha 4\beta 7$  integrin and is a gastrointestinal system (GIS)-selective integrin inhibitor. In contrast to anti-TNFs having the potential of activity at any inflammatory foci, VDZ targets intestinal inflammation alone, and this feature limits its use in clinical practice. However, high GIS selectivity is the reason why cases of PML associated with natalizumab have not been seen with VDZ. Currently, no cases of PML have been reported with VDZ either globally or in Turkey. Therefore, regarding the current practice in Turkey, the abolishment of prescription requirement of being signed by a neurologist would be more convenient for patients and would reduce labor loss. There are no such requirements in many countries where VDZ is available.

The current place of VDZ in the reimbursement system of our country is after anti-TNF failure or intolerance in CD. Although VDZ has been mainly used after anti-TNF failure based on real-world data, favorable sustained remission rates have raised the topic of use of VDZ after conventional treatment (31,98,99). Prior anti-TNF agent use, perianal involvement, current smoking has a negative impact on treatment response (98). Actually, this real-world experience is applicable to all biologic agents. Real-world data

**Table 5.** Clinical studies of biologics.

Study	Biologic	Treatment phase	Study information reference	No. Of patients	Dose	Clinical response	Clinical remission
ACCENT-I	Infliximab	Induction and maintenance	R, DB, III (114)	573	(Induction: all patients, 5 mg/kg week 0) Group 1: placebo Group 2: 5 mg/kg Group 3: 10 mg/kg	58% at week 2	At week 30 Group 1: 21% Group 2: 39% Group 3: 45%
SANDS BE et al. (2004)	Infliximab	Fistula closure in Crohn's disease	R, DB, III (104)	306	(All patients 5 mg/kg weeks 0, 2, and 6) Group 1: placebo Group 2: 5 mg/kg every 2 months	69% at Week 14	Fistula closure at week 54 Group 1: 19% Group 2: 36%
CLASSIC-I	Adalimumab	Induction, comparisons of dosing schedules	R, DB, III (115)	299	Group 1: placebo Group 2: 40 mg/20 mg (weeks 2-4) Group 3: 80 mg/40 mg (weeks 2-4) Group 4: 160 mg/80 mg (weeks 2-4)	-	At week 4* Group 1: 12% Group 2: 18% Group 3: 24% Group 4: 36%
CHARM	Adalimumab	Induction and maintenance comparisons of dosing Schedules	R, DB, III (116)	854**	(All patients week 0: 80 mg, week 2: 40 mg) Group 1: placebo Group 2: 40 mg (every 2 weeks) Group 3: 40 mg (every week)	91% at week 4	At week 56 Group 1: 12% Group 2: 36% Group 3: 41%
PRECISE-II	Certolizumab	Induction and maintenance	R, DB, III (117)	668	(All patients 400 mg weeks 0, 2, and 4) Group 1: placebo Group 2: 400 mg/month	64% at week 6 At week 26 Group 1: 36% Group 2: 63%	At week 26 Group 1: 29% Group 2: 48%
GEMINI-II	Vedolizumab	Induction and maintenance comparisons of dosing Schedules	R, DB, III (118)	368,747***	368 patients (induction) Group 1: placebo Group 2: vedolizumab	Induction: week 6 Group 1: 6.8% Group 2: 14.5%	Maintenance: Every 8 weeks Group: 39% Every 4 weeks Group: 36.6% Placebo: 21%,6
UNITI I-II-IM#	Ustekinumab	Induction and maintenance comparisons of dosing schedules	R, DB, III (119)	UNITI-I: 741 UNITI-II: 628 UNITI-IM: 397	UNITI-I, II: 130 mg, 6 mg/kg, placebo UNITI-IM: 90 mg 8 weeks or 12 weeks	Induction: week 6 34.3%, 33.7%, 21.5%, 51.7%, 55.5%, 28.7%, respectively (UNITI-I, II)	Maintenance: (UNITI-IM) week 44 Placebo: 35.9% Every 8 weeks: 53.1% Every 12 weeks: 48.8%

\*CDAI &lt;220.

\*\*Clinical response criteria: CDAI &gt;70 regression. Patients with clinical response (778/854; 91%) were divided into groups.

\*\*\*In the Gemini study, 368 patients received placebo or VDZ in the induction phase, 747 patients received open label 300 mg VDZ at 0 and 2 weeks, and then patients with clinical response (n=461) received 300 mg as maintenance at week 4 or week 8.

#741 anti-TNF refractory or intolerant patients were included in the UNITI-I study, 628 patients refractory or intolerant to conventional treatment were included in the UNITI-II study, and 397 patients who had response were included in the UNITI-IM study.

R: randomized; DB: double blind.

suggest that VDZ is as effective as anti-TNF agents following the failure of conventional treatment (99). In a study presented in ECCO 2018, better 12-month remission rates were reported with VDZ, particularly in colonic involvement, in 538 patients matched for demographics and risk groups (100). Therefore, VDZ may be used after conventional treatment in patients with CD with colonic involvement but without extraintestinal manifestations. Optimum response is achieved at approximately 12-16 weeks after the onset of the treatment, and any decision of non-response should not be made before week 24, particularly in patients with limited treatment options (98). Although it may appear logical to add low-dose immunomodulatory therapy to VDZ to prevent the development of antibodies, there is no sufficient evidence about this subject.

In a meta-analysis assessing the side effects associated with VDZ, no increases were observed with respect to important side effects, such as mortality, cancer, progressive multifocal leukoencephalopathy (PML), and serious infections (60,101). Owing to the low potential of infection side effects, VDZ and ustekinumab may be preferred in patients who are considered to be susceptible to infectious side effects (60,101,102).

- Although VDZ is generally used in CD after anti-TNF failure, it has been increasingly used as first-line biologic treatment after conventional treatment failure.
- The effect of VDZ was found to be superior in anti-TNF naive patients than in anti-TNF experienced patients.
- As the effects of VDZ appear late, one should wait 24 weeks at least to consider treatment failure particularly in patients with limited treatment options.
- Hypothetically, GIS selectivity of VDZ may prevent it from being effective in extraintestinal manifestations of IBD.
- VDZ and ustekinumab appear to be safer than anti-TNF agents with respect to infectious side effects.

### **Ustekinumab in the management of CD**

Ustekinumab is a humanized IgG1 antibody targeting the p40 subunit of interleukins 12 and 23. It has been initially approved by the Food and Drug Administration (FDA) for the treatment of psoriasis. In a study in either primary or secondary non-responders to anti-TNF therapies, ustekinumab was found to be superior than placebo in both inducing and maintaining remission (103).

Ustekinumab is not reimbursed for the treatment of CD in our country. Therefore, it is used off-label to treat patients who have not responded to other biologic therapies. There are no studies comparing ustekinumab and VDZ after anti-TNF failure. However, ustekinumab may be preferred when a rapid onset of action is required and in patients with CD associated with extraintestinal manifestations or coincidental psoriasis (104).

Phase studies and real-world data indicate that ustekinumab is safe and ustekinumab is associated with fewer infection side effects than anti-TNF agents (102).

Long-term, head-to-head comparative studies are needed to provide an appropriate response to "Whether VDZ or ustekinumab should be used in CD following conventional treatment failure?".

A group of biologic agents that will have less or no impact on the effects of other biologics should be primarily preferred following conventional treatment. Although anti-TNF part of this issue is partially known, there is no answer to this question yet.

- Ustekinumab may be preferred when a rapid onset of action is required and in patients with CD associated with extraintestinal manifestations or coincidental psoriasis.
- There are no head-to-head comparative studies investigating ustekinumab versus VDZ following anti-TNF agents.

### **Use of biologics in patients with CD who present with complex perianal fistula**

Perianal involvement is one of the major risk factors for poor prognosis. Considering all treatment options, clinical and endoscopic response rates are lower in these groups of patients than in other groups. Therefore, particularly in the presence of other risk factors, it appears to be rationale to initiate anti-TNF therapy in combination with conventional treatment in patients with perianal involvement, if not contraindicated.

Biologic agents have been proven to be superior over placebo in perianal fistula healing based on subgroup analyses of phase studies. Furthermore, infliximab has been investigated in randomized, controlled, prospective studies (105,106). However, because of the inadequacy of parameters for fistula closure, whether these findings indicate a favorable long-term outcome and their sustainability have not been investigated.

The inclusion of antimicrobial therapy into the management plan may occasionally increase treatment success, although it can be transient. Complex nature of the fistula, age of the patient, and concurrent abscesses may have a negative impact on treatment success. In case of the presence of an abscess in fistulizing CD, anti-TNF therapy should be initiated under antimicrobial therapy after the abscess is drained and a seton should be placed to prevent the development of new abscesses.

- Perianal involvement is one of the major risk factors for poor prognosis.
- Biologic agents and particularly infliximab have been proven to be more effective than placebo in the clo-

sure of perianal complex fistula in short term and intermediate term.

- Combined use of biologics and antimicrobial therapy increases the chance of treatment success.
- In the presence of an abscess, anti-TNF therapy should be given under antimicrobial therapy after the abscess is drained and a seton is placed.

### **The use of biologics in CD after surgical resection**

The requirement for surgical treatment is diminished after the introduction of biologic agents in the treatment of CD (107,108). The 5-year clinical recurrence rate is approximately 50%, and the endoscopic recurrence rate is approximately 90% following surgery (109). However, it remains unknown what is the real meaning of post-resection endoscopic score and how much it really figures out a progressive process. Furthermore, observational comments on anastomosis ulcers rather highlight the local ischemic process and may not show any progression further. Risk factors for developing postoperative recurrences include penetrating disease behavior, current smoking, and history of second surgical resection (110).

During the postoperative period in CD, the main treatment strategy recommended by the guidelines has been to prevent disease recurrences (31,110). Although the efficacy of 5-ASA was low in studies, it has been widely used during the postoperative period owing to its high safety profile (111). Guidelines recommend the use of AZA and/or anti-TNFs in patients at high risk of recurrence based on a low evidence level. Although metronidazole and ornidazole have a partial effect on the prevention of recurrence, this effect is not long lasting, and toxicity is a major concern (112).

The reason of starting prophylactic treatment during the postoperative period is to prevent bowel damage and, subsequently, to protect patients from additional surgery, function loss, and comorbidity. On the other hand, although meta-analyses demonstrated a limited benefit of AZA and anti-TNF therapy, there are conflicting data on their effect on the prevention of postoperative clinical recurrences (113,114). Another important consideration is that the medication will not provide any further benefit in patients who develop recurrence under prophylaxis and this means further restriction in treatment options which are already restricted in these patients.

Therefore, a close monitoring is recommended using combined parameters, such as clinical signs and symptoms, intestinal ultrasound, calprotectin, acute phase, and colonoscopy, when required. Treatment should be given in an accelerated manner from local treatment to biologics. Intensive treatment appears to be more appro-

priate in patients with residual active disease segment after surgery and those who have undergone re-surgery. Although IM and anti-TNF therapies may not prevent surgery, they may be beneficial during the postoperative period (115).

- Risk factors for postoperative recurrences include penetrating disease behavior, current smoking, and a history of prior surgical resection.
- Guidelines recommend the use of AZA and/or anti-TNFs in patients at high risk of recurrence based on a low evidence level.
- Close monitoring using multiple parameters and accelerated treatment is recommended regarding disease recurrences during the postoperative period.
- Even though a TNF agent fails preoperatively, it should be used for prophylaxis and in disease activation.

## **SECTION 6**

### **How to monitor patients using biologic therapies**

Patients with IBD should be carefully monitored during the treatment. Phenotype of disease, activity (active (mild-moderate-severe) or remission), extraintestinal involvement, and complications must be evaluated at each outpatient visit. In routine daily practice, it might be difficult to calculate clinical activity index, such as CD Activity Index (CDAI) and UC activity index (Mayo score or True-love and Witz severity index or clinical activity index). We can estimate the disease activity according to symptoms and laboratory results (Table 6) (122).

The simple clinical colitis activity index (SCCAI) can be helpful in UC. The SCCAI is composed of six items: bowel frequency during the day, bowel frequency during the night, urgency for defecation, blood in stool, general well-being, and extraintestinal manifestations (arthritis, erythema nodosum, pyoderma gangrenosum, and uveitis). Clinicians are able to categorize two types of patients based on the SCCAI: patients with inactive disease (SCCAI score <5) and patients with active disease (SCCAI score ≥5). Bowel movements >3 times during the night, bloody stool, and presence of any extracolonic manifestations represent active disease (123,124).

Evaluation of biologic therapy response in every visit is mandatory. Follow-up visits should be done every 2 or 3 months depending on which biologic is being used.

Clinical response should be evaluated according to the CDAI or Harvey-Bradshaw index in CD. Treatment response is defined as a decrease of 70-100 points from the baseline CDAI. Remission is accepted as CDAI scores <150 points. Relapse is defined as a flare of symptoms

(CDAI >150 points) in clinical remission during the follow-up period. Early relapse is accepted as any relapses within 3 months. Relapse can be rare (<1/year), frequent (>1/year), or continuous (31). In every flare, complications must be evaluated. If there is a complication, such as bowel perforation, persistent or recurrent obstruction, abdominal abscess not amenable to percutaneous drainage, intractable hemorrhage, dysplasia/cancer, or medically refractory disease, surgery is indicated. Surgery can be an alternative in localized disease (<30 cm) instead of medical treatment change (42).

In every visit, evaluation should be based on clinical, laboratory (CRP, whole blood test, and fecal calprotectin), and/or imaging, when clinically needed (computerized tomography/magnetic resonance imaging/ultrasound, endoscopy), if applicable (31). Clinical response can be evaluated by the SCCAI in UC. We have to consider the impact of disease on the patient (symptoms, life quality, fatigue, and disability), complicated disease course (anatomic damage, resection, perianal disease, frequency of flare, and extraintestinal involvement), and presence of inflammation (CRP, mucosal lesions, upper GIS involvement, and disease extent) (125). Biomarkers, such as fecal calprotectin, are important for the management of disease. The cut-off level should be accepted as <150 µg/g for fecal calprotectin. Presence of complications related to the disease or drugs must be carefully evaluated. If any complication is detected, we have to discontinue the biologic treatment.

In routine practice, endoscopic evaluation should be classified as follows: mild, edema/erythema; moderate, erosion and superficial ulcers (involved surface 10%-30%); and severe, deep large ulcers >2 cm. Evaluation of the ileum for postoperative endoscopic recurrence by colonoscopy within a year (generally after 6 months) after ileocolonic resection may help guide further therapy. Postoperative endoscopic evaluation must be rated by the Rutgeert's scoring system (126).

The rate of loss of response to anti-TNF is approximately 30%-40% annually. Primary non-responder rate is 20%-30%. Therefore, evaluation of the response to biologic treatment is important to prevent the unnecessary use of biologic agents (127). Clinical response is generally observed during 2-4 weeks. The maximum waiting period for clinical response must be 12-16 weeks. If induction of remission is successful, maintenance therapy will continue. *Clostridium difficile*, cytomegalovirus, and enteric pathogens must be analyzed in refractory patients during the induction therapy (31). Biologic drug failure can occur via three mechanisms:

- Mechanistic failure: absence of antidrug antibody, enough trough level (*change the class*)

- Immune-mediated drug failure: antidrug antibody positive, low or undetectable trough concentrations (*add immunomodulator or switch anti-TNF*)
- Non-immune-mediated drug failure: subtherapeutic drug trough concentrations and absent antidrug antibodies (*increase the dose*).

Therapeutic target trough levels for anti-TNF were accepted as follows: infliximab >7.5 µg/mL, adalimumab >5 µg/mL, and certolizumab pegol >20 µg/mL (31).

Non-inflammatory causes (abscess, infections, stricture, and cancer) must be kept in mind in primary or secondary non-responder patients (128). Proactive anti-TNF drug monitoring does not increase clinical remission or prevent the loss of response (129). Trough levels were negatively correlated with CRP levels (130). Serum drug levels should be monitored in primary non-responder patients or in patients with loss of response to anti-TNFs, if applicable. A recently published study showed that any increase in the infliximab dose must be based on symptoms. Drug levels and antibody monitoring have no additional benefits for the CS-free clinical remission in a larger proportion of patients (131). On the other hand, fecal calprotectin is informative in predicting relapse and primary non-response to anti-TNF therapy in IBD (132). The rate of the discontinuation of treatment because of adverse events is higher in the combination therapy (at least 3 drugs) (odds ratio=3.225, p<0.001). The rate of anti-TNF discontinuation because of adverse events is approximately 10%-20% (133). Exposure to different types of biological treatments is associated with specific changes in immune profiles (134). We have to evaluate all possible clinical conditions (e.g., hypoalbuminemia, smoking, primary non-responder, and non-inflammatory reasons) for non-responder patients. In addition to the routine biochemical analyses and whole blood test, LDH and protein electrophoresis must be included in the laboratory workup in every follow-up visit. Lymphoma risk is high, especially in combination therapies in very young (<18 years) or elderly patients (>65 years) (42). A careful physical examination is mandatory during the biologic therapy.

Endoscopic evaluation is helpful for the management of disease. There is no clear suggestion for timing. After 6-12 months of biologic therapy, endoscopic evaluation can be performed. If the patient is symptomatic and there is a mucosal lesion, therapy should be revised. Although the patient is asymptomatic, mucosal lesion can be seen. In this clinical condition, we can discuss for therapy change with the patient. However, we must not forget that the clinical and endoscopic remission rate is 40% for anti-TNFs and a deep remission rate is 30% (135). We have to answer many questions, if we perform routine follow-up endoscopy in asymptomatic patients

**Table 6.** Clinical activity estimates for Crohn's disease according to symptoms and laboratory workup.

Mild (CDAI 150–220)	Moderate (CDAI 220–450)
√ No obstruction, fever, dehydration, abdominal mass, and tenderness	√ Intermittent vomiting
√ Elevated CRP	√ Weight loss >10%
√ Weight loss <10%	√ Abdominal tenderness without obvious ileus and abdominal mass
Severe (CDAI >450)	
√ Refractory symptoms in spite of the effective therapy	
√ Cachexia (BMI 18 kg/m <sup>2</sup> ) or presence of obstruction, abscess	

during treatment with biologic treatment (cost-effectivity, informed consent of patients, and interval of endoscopy). On the other hand, we have to perform colonoscopy for colon cancer surveillance according to the guidelines (every 1 or 2 years) in UC and CD.

As a summary,

- Evaluate clinical response to therapy
- Clinical follow-up visit should be performed every 2-3 months (effectivity/adverse events)
- In asymptomatic patients, wait and observe clinical/laboratory findings
- Surgery must be advised when needed.

## SECTION 7

### **Should we stop biologics? If yes, when and how?**

Since late 1990s, evolving therapies, such as anti-TNFs, for CD and UC have been increasingly used. Whereas there is almost a consensus in which patients to start anti-TNF, when to start biologics or how to start biologics, it is not clear yet when to stop such kind of treatments or even in which patients with inflammatory diseases (IBD) we can stop these medications. Once these medications have gained popularity, concerns have been raised about their possible side effects. Most bothersome side effects include serious infections and opportunistic infections (45,136), melanoma/non-melanoma skin cancers (137), and lymphoproliferative disorders (138). In patients under combination treatments consisting of TPs and anti-TNFs, these risks are even higher (45,136).

Other reasons which give rise to thought of quitting anti-TNFs are increased healthcare costs or national regulations and some specific situations, such as pregnancy. Despite the arguments in favor of stopping anti-TNFs, there is no consensus yet on in which patients we can stop or de-escalate anti-TNFs because of loss of efficacy concerns. In an observational study from England, the authors showed relapse rates of 36% in CD and 42% in UC 1 year after the discontinuation of anti-TNF therapy (139).

In another prospective, multicenter, observational study from Czech Republic in 78 patients with IBD in off-steroid clinical and endoscopic remission, anti-TNF therapy was stopped, and patients were followed up. 53% of patients with CD and 53% of patients with UC relapsed by the end of the follow-up period with a median time to relapse of 8 months in CD and 14 months in UC, respectively (140).

Knowing that there is an increased risk of relapse after the discontinuation of anti-TNFs, there is an absolute need to clarify the determinants of the risk of relapse. A recent review evaluating the factors associated with the risk of relapse after stopping anti-TNFs in patients with IBD revealed that younger age, smoking, longer disease duration, perianal fistulizing disease, low hemoglobin levels, high leucocyte counts, high fecal calprotectin levels, and high serum anti-TNF levels were found to be the factors associated with higher relapse rates, whereas mucosal healing appeared to be protective against relapse (141). Another review regarding factors predicting relapse after the discontinuation of anti-TNFs showed that elevated fecal calprotectin, elevated CRP and leucocyte count, absence of mucosal healing, smoking, perianal disease, young age at diagnosis, disease location (ileocolonic disease), male sex, elevated trough levels, prior anti-TNF use, and prior immunomodulatory failure might be associated with higher relapse rates (142). Another study showed that ileocolonic disease, prior anti-TNF use, and prior bowel surgery might increase the risk for relapse after the discontinuation of anti-TNF therapy (140).

The French inflammatory bowel diseases group (GETAID) performed a prospective study to investigate potential associations between demographic, clinical, and biologic factors and the time to relapse using a Cox model. Parameters included in the analysis were as follows: male sex, CS use, previous surgical resection, hemoglobin level, leucocyte count, CDEIS scores, hs-CRP levels, infliximab levels, and fecal calprotectin levels. The authors produced a model assessing the risk for relapse. According to these

models, patients with <4 factors appeared to have a relapse risk of <20%, whereas patients who had >6 factors had a 100% likelihood of relapse (143).

Overall, mucosal healing appears to be one of the most important factors preventing disease flare after stopping anti-TNFs. In CD, the discontinuation of anti-TNF therapy based on clinical remission alone is associated with a relapse rate of 42% after 1 year of follow-up, whereas this rate is reduced to 26% when such decision is based on both clinical remission and endoscopic remission (144). Similar differences were also observed among patients with UC. Relapse rates were 50% and 33%, respectively, after discontinuation based on clinical remission or endoscopic remission alone in patients with UC (144).

A European expert panel discussing when to stop biologic treatment in CD safely came to a conclusion as withdrawal of anti-TNF monotherapy should be considered after 2 years in case of both clinical remission and mucosal remission are achieved or after 4 years of clinical remission. The same panel reached to a conclusion for patients treated with combination treatment including anti-TNFs and immunomodulatory drugs that the withdrawal of anti-TNF therapy should be considered after 2 years of clinical remission (145).

In a recent review, the authors proposed a risk-based de-escalation algorithm (146). According to this algorithm, if the patient is receiving steroids, immunomodulatory, and anti-TNF agents, we should stop CSs. If a low-risk patient is receiving immunomodulatory and anti-TNF agents, we should stop immunomodulatory agents, whereas in high-risk patients, we should continue the combination treatment. If a patient is receiving monotherapy, we might stop anti-TNFs in case of deep remission especially in an elderly patient. In another study (147), the author described patient profiles favoring treatment continuation and profiles favoring treatment withdrawal. According to this study, factors favoring continuation include young age with extensive or complicated disease, patients with complex perianal CD, patients with extensive UC, patients with previous surgeries, persisting endoscopic lesions, or elevated CRP and/or fecal calprotectin in patients with CD. Factors favoring treatment withdrawal are older age without previous surgeries, old age with limited extent of UC, side effects related to anti-TNFs, absence of residual trough level, and poor adherence to medication.

A brief summary of risk factors are summarized in Table 7.

In summary,

1. Following the discontinuation of anti-TNF agents in patients in clinical remission, approximately half of the patients will relapse.

2. Before deciding when to stop anti-TNF, it is recommended to classify patients with IBD into low risk for relapse and high risk for relapse groups.
3. Clinical factors regarding high risk for relapse are young age, previous surgeries, ileocolonic involvement in CD and extensive colitis in UC, and complex perianal fistulas in CD.
4. Combining endoscopic assessment, fecal calprotectin and anti-TNF trough levels with clinical factors listed above will help to determine low- or high-risk patients more precisely.

## SECTION 8

### New upcoming treatments in IBD

Anti-TNF agents are the most widely used biologic agents in the treatment of IBD. These agents have been shown to be steroid-sparing, to reduce IBD-related hospitalizations and surgeries, induce mucosal healing, and improve patients' quality of life. However, these treatments are not effective in all patients, and some patients may not respond to the treatment (40%) or some patients who respond to this treatment can lose their response over time (10%-45%) (104). These agents are well-tolerated, but their use can be associated with some adverse effects, such as a risk for infections especially tuberculosis and a risk for malignancy, such as non-Hodgkin lymphoma and non-melanoma skin cancers (148).

Several novel agents targeting different inflammatory pathways in IBD are available or under investigation. Two new classes of biologic drugs, integrin-antagonists for both UC and CD, and an interleukin (IL)-12/23-antagonist ustekinumab for CD are now available. The first Janus kinase (JAK) inhibitor, tofacitinib, for UC will enter the market in the near future. In the present study, ustekinumab, anti-IL23 agents, JAK inhibitors, and sphingosine-1-phosphate receptor modulators will be discussed in detail.

### Anti-IL12/IL23 agents

#### Ustekinumab

Ustekinumab (Stelara®, Janssen) is a monoclonal IgG1 antibody targeting the p40 subunit of IL-12 and IL-23 which leads to a downregulation of cytokine expression in both Th1 and Th17 pathways (149-151) (Figure 2). It was recently approved for the treatment of moderately to severely active CD on the basis of the demonstrated efficacy in induction (UNITI-1 and UNITI-2) and maintenance (IM-UNITI) studies in both TNF antagonist naive patients and patients who fail to respond to a TNF antagonist (152,153).

Patients in the 8-week UNITI-1 and -2 induction trials were randomized at week 0 to receive a single iv infusion of ustekinumab at a dose of 130 mg, a single iv infusion of

ustekinumab at a dose of ~6 mg/kg body weight or placebo (154).

In the UNITI-1 study (n=741), ustekinumab induced clinical remission in 18.5% of patients who failed to respond or who were intolerant to anti-TNF at week 6 (vs. 8.9% of patients on placebo,  $p=0.002$ ) and in 20.9% of these patients at week 8 (vs. 7.3% of patients on placebo,  $p<0.001$ ). In the UNITI-2 study (n=638), ustekinumab led to a higher rate of clinical remission at week 6 (34.9% vs. 17.7% in the placebo arm,  $p<0.001$ ) and week 8 (40.2% vs. 19.6% in the placebo arm,  $p<0.001$ ) in anti-TNF naive patients. In the pooled UNITI-1 and UNITI-2 population (n=155), ustekinumab induced a greater reduction in SES-CD than placebo (n=97) from baseline to week 8 (-2.8 vs. -0.7,  $p=0.012$ ), thus showing the effect of ustekinumab on mucosal healing (154).

Patients who completed the UNITI-1 or -2 studies could progress to the IM-UNITI maintenance trial at week 8. The IM-UNITI study showed that two-thirds of patients on ustekinumab had sustained clinical remission at week 44 (vs. 45.6% of those on placebo,  $p=0.007$ ) (155). Ustekinumab was generally well-tolerated as either induction or maintenance therapy; serious infections and malignancies were rare (154,155).

### **Anti-IL23 agents**

Increased knowledge on the role of IL-23 has allowed for the development of effective therapeutic progresses by blocking the IL-23 mediated pathways (156). These more selective anti-IL23 p19 agents are:

- Brazikumab (MEDI2070, formerly AMG139, Allergan)
- Risankizumab (BI655066, ABBV066, AbbVie)
- Guselkumab (CNTO1959, Janssen)
- Tildrakizumab (MK3222, Merck&Co.)
- Mirikizumab (LY3074828, Eli Lilly) (147,149-151,154).

Two multicenter, randomized, placebo-controlled phase II clinical trials have evaluated risankizumab and brazikumab (157). The humanized IgG1 monoclonal antibody risankizumab was tested in a randomized, double-blind, placebo-controlled phase II study (n=121) in moderately-to-severely active CD. Patients were randomized equally to receive iv 200 mg of risankizumab, 600 mg of risankizumab, or placebo at weeks 0, 4, and 8. The 600 mg risankizumab dose achieved significantly higher clinical (37% vs. 15.0%,  $p=0.0252$ ) and endoscopic remission (20% vs. 3.0%,  $p=0.0107$ ) rates at week 12 (158).

Another humanized monoclonal antibody brazikumab was evaluated in a double-blind, placebo-controlled phase II trial (n=119) in patients with moderate to se-

vere CD who had failed to respond to a TNF antagonist. Patients were randomly assigned to receive either brazikumab (700 mg) or placebo iv at weeks 0 and 4. A clinical response was achieved in 49.2% of patients who received brazikumab at week 8 compared with 26.7% of those assigned to placebo ( $p=0.010$ ) (159). Confirmatory phase 3 studies are underway.

Mirikizumab is currently being studied in two phase II trials including patients with CD. Two other IL-23 p19 antibodies, tildrakizumab and guselkumab, are also likely to be studied for IBD in the future (153).

### **JAK inhibitors**

JAKs are a family of intracellular protein tyrosine kinases: JAK1, JAK2, JAK3, and tyrosine kinase 2. These are crucial to the downstream regulation of inflammatory mediators. Transcription factor STATs (signal transducer and activation of transcription) are activated by binding to transmembrane receptors. JAK inhibition results in suppression of B and T cells but retains regulatory T cell function, therefore, is an important target in IBD (160).

### **Tofacitinib**

Tofacitinib (Xeljanz, Pfizer) is an orally administered small molecule that predominantly inhibits JAK1 and JAK3 (161) (Figure 3). Recent phase III data showed a significant treatment effect in three clinical trials in UC (162).

In the induction trials (OCTAVE 1 and OCTAVE 2), 598 and 541 patients, respectively, were randomly assigned to receive induction therapy with tofacitinib (10 mg twice daily) or placebo for 8 weeks. Clinical remission occurred in 18.5% of the patients in the 10 mg tofacitinib at week 8 group versus 8.2% in the placebo group ( $p=0.007$ ) in the OCTAVE 1 trial and in 16.6% versus 3.6% ( $p<0.001$ ) in the OCTAVE 2 trial. Patients who completed induction trials with a clinical response were participated in the OCTAVE SUSTAIN trial. In this trial, remission at week 52 occurred in 34.3% (5 mg) and 40.6% (10 mg) versus 11.1% in the placebo group ( $p<0.001$ ) (153,160,162,163).

### **Filgotinib**

Filgotinib (Galapagos; GLPG0634, GS-6034) which is a JAK1-selective inhibitor was investigated in a phase II study in CD showing positive results at week 10. 47% of patients treated with 200 mg filgotinib daily achieved clinical remission (vs. 23% treated with placebo,  $p=0.0077$ ) (163-165). Further trials in fistulizing CD and small bowel disease, as well as phase III trials in UC and CD, are underway (153-163).

### **Upadacitinib**

Preliminary results of a phase II study in CD with JAK1-selective inhibitor upadacitinib (ABT-494, AbbVie) showed higher rates of endoscopic remission (with 24 mg at week

**Table 7.** Risk factors for relapsing disease after stopping medical treatment.

	Favoring high risk for relapse	Favoring low risk for relapse
Age	Young	Elder
Previous surgery	Yes	No
Prior anti-TNF use	Yes	No
Complex perianal disease	Yes	No
Extensive ulcerative colitis	Yes	No
Anti-TNF naïve	No	Yes
Elevated fecal calprotectin	Yes	No
High anti-TNF trough levels	Yes	No
Endoscopic remission	No	Yes
Male sex	Yes	No

16, 22 vs. 0% in the placebo group,  $p=0.01$ ) and clinical response (with 6 mg and 24 mg twice daily, 57% and 61% respectively, vs. 32% with placebo,  $p=0.05$ ) than placebo (166). The drug is being evaluated for UC and in an upcoming phase III trial for CD (153,163).

### **Sphingosine-1-phosphate receptor modulators**

Naïve T cells routinely circulate between the blood and lymphatic tissue. They enter the lymph nodes through high endothelial venules and egress through the efferent lymphatic vessel into the bloodstream. The sphingosine-1-phosphate (S1P) receptor family consists of five receptors (S1P1-S1P5). The egress process is governed by interactions between S1P1 receptors on lymphocytes and their ligand S1P which is expressed on the cell surface of lymphatic endothelial cells. Upon stimulation, the cell surface-associated S1P receptors become degraded, leading to sequestration of B and T lymphocytes in the peripheral lymphoid organs and reduced trafficking of these cells to inflamed tissue (149).

### **Ozanimod**

Ozanimod (RPC1063, Celgene), oral S1P receptor 1 and 5 agonists, demonstrated efficacy in a phase II clinical trial for the treatment of UC (167). 197 patients were randomly assigned to receive either placebo or 0.5 or 1 mg of oral ozanimod daily. The 1 mg dose group showed higher rate of clinical remission than the placebo group (16 vs. 6%,  $p=0.048$  at week 8 and 21 vs. 6%,  $p=0.01$  at week 32). Ozanimod is currently being tested in a phase III trial in UC and a phase II trial in CD.

Another selective S1P modulator, *etrasimod* (APD334), is being evaluated in a placebo-controlled phase II trial in UC (153,168).

## **SECTION 9**

### **Use of conventional and biological agents in the management of IBD in special conditions including pregnancy, lactation, and malignancy**

Pregnancy, breastfeeding, and a history of malignancy are usually among the exclusion criteria in phase studies of drugs and important clinical studies. Pregnant patients usually receive additional drugs for the treatment and control of their disease, other than those which are under investigation for fetal toxicity. Occasionally, IBD or rheumatic diseases themselves may harm the unborn child.

In a similar way, the incidence of certain cancer types is increased during the course of IBD and rheumatic diseases. As a result, investigating a drug in pregnant or lactating patients or in patients with a history of malignancy means additional investigation of many complex confounding factors and, consequently, a slow accumulation of information.

### **Use of conventional therapy during pregnancy and lactation**

**Methotrexate:** Fetal malformations have been observed in patients who got pregnant during treatment with MTX (167). MTX should be discontinued immediately in patients who got pregnant during treatment with MTX, and folic acid supplementation should be started. Pregnant patients exposed to MTX should be followed up by experienced physicians at an obstetrics clinic. Washout period for MTX should be 3 months in women who are planning to conceive. MTX should be switched to pregnancy-safe alternatives 3 months before conception, and folic acid supplementation should be started (170).

MTX is excreted into human milk in small amounts; however, available information about its use during lac-

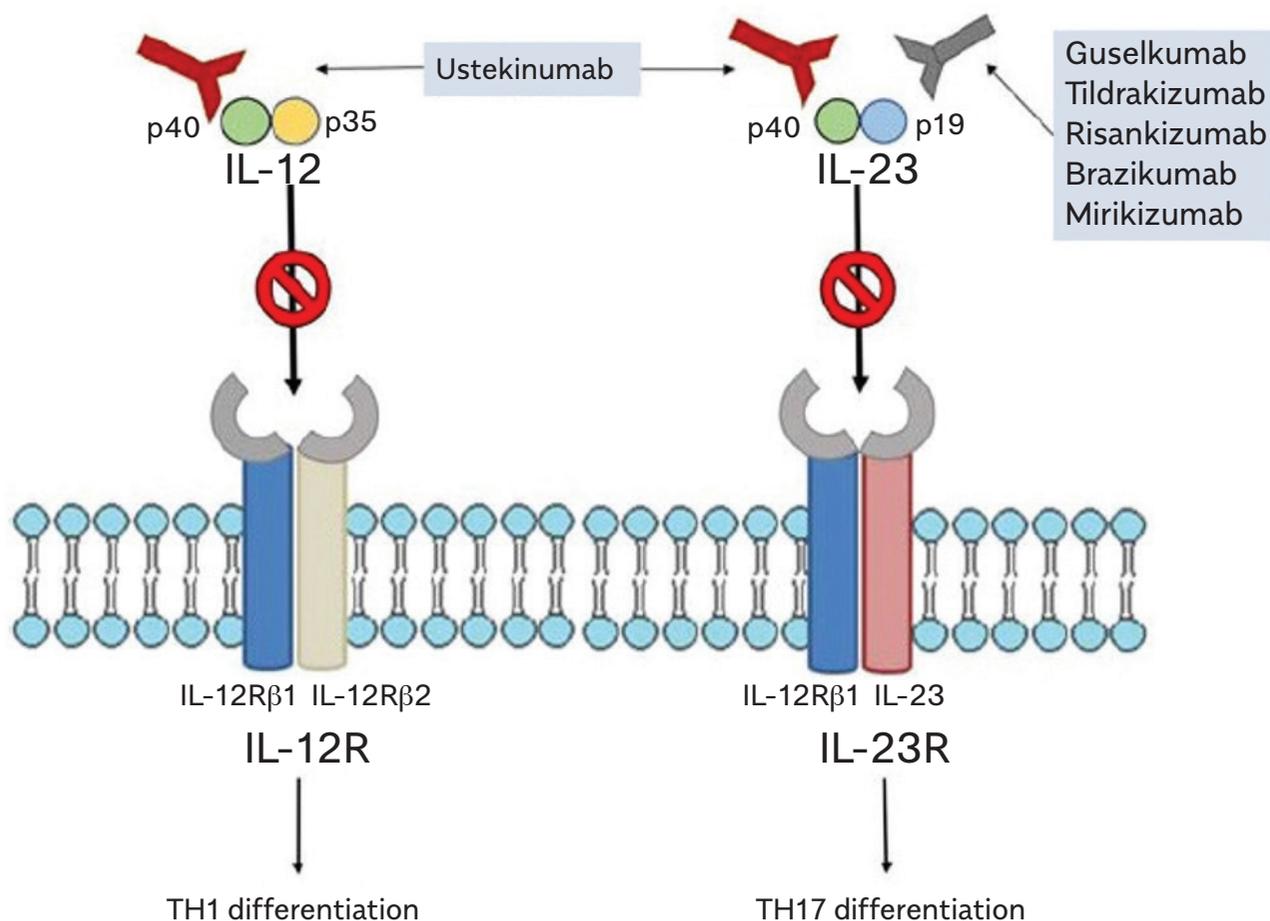


Figure 2. Molecules targeting IL-12/IL-23 axis in IBD (148).

tation is limited (171). Lactating mothers should not use MTX.

Paternal low-dose MTX appears to be safe (172). However, potential adverse effects associated with weekly doses >20 mg on sperm quality should be kept in mind.

**AZA, 6-MP:** A number of studies have investigated the use of TPs in pregnancy, and this group of drugs has been found to be safe during pregnancy and lactation, in general (173-175). The use of AZA during pregnancy has been linked to low birth weight in certain studies; however, a meta-analysis suggested that low birth weight might be associated with disease activity rather than exposure to AZA during pregnancy (176). It is not known whether the incidence of any diseases is increased in the adulthood or in the old age in children born to women exposed to AZA during pregnancy. In conclusion, considering risk/benefit balance, low-dose AZA (<2 mg/kg) may be used during

pregnancy. Measurements of enzyme activity are rather important in these patients.

AZA and its metabolites are excreted into human milk in small amounts, and AZA metabolites were not found in serum samples of infants breastfed by mothers who were taking AZA (177,178). Therefore, the use of AZA in lactating mothers is considered safe; however, long-term outcomes are not known. In general, cessation of lactation is not recommended in lactating mothers who are on AZA (171,179). Paternal exposure to low-dose AZA is safe (180).

**Corticosteroids:** Steroids can cross the placenta; however, fetal exposure is very low as maternal steroids are metabolized in the placenta (180). Although steroids do not cause major congenital defects, certain studies have demonstrated a potential increase in the prevalence of cleft lip and palate, in line with animal studies (181). On the other hand, some studies failed to demonstrate any asso-

ciations between CSs and these abnormalities (182,183). In conclusion, prednisolone, methylprednisolone, and oral budesonide may be used in the management of IBD at any stages of pregnancy, and any increase in the risk for major fetal malformations is not expected (171,180,184). Study results on whether there is an increased risk for cleft lip and palate are conflicting, but mostly favor no association. Steroids used in the management of IBD are safe for paternal use (185).

**5-ASA and SASP:** Although an association was found between the use of 5-ASA and premature births, in certain studies, disease activity is a major confounder in these studies (186). A meta-analysis failed to show any association between the use of 5-ASA and the risk for fetal malformation, premature birth, or abortions (187). Concerns have been raised about the potential negative impact on fetal neurological development caused by dibutyl phthalate (DBP), a substance which provides 5-ASA tablets with delayed release characteristic (188). 5-ASA formulations which contain this substance should be avoided during pregnancy. 5-ASA formulations available in our country do not contain DBP. 5-ASA can be used at any stages of pregnancy.

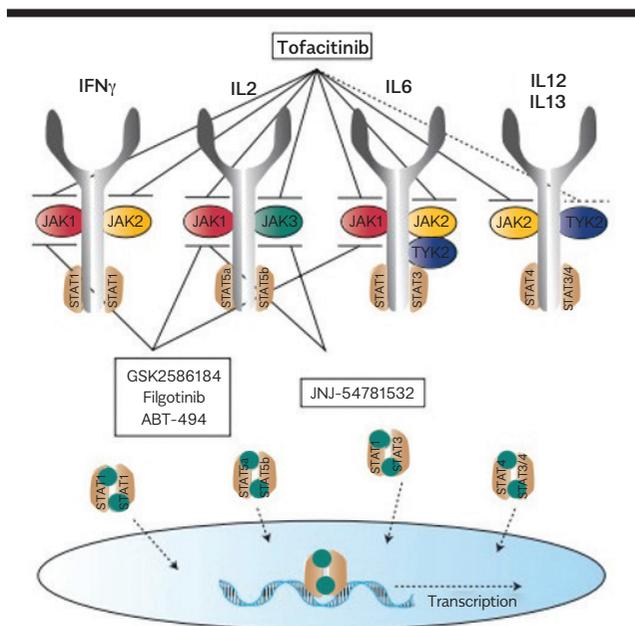
SASP can also be used during pregnancy (189). Sulfapyridine, the moiety of the product responsible for folic acid deficiency, is a sulfonamide antibiotic. Therefore, folic acid supplementation is required during pregnancy, particularly in the first trimester (189).

SASP and 5-ASA are safe in lactating mothers (190-192). They should be kept in mind as a rare cause of diarrhea in newborn.

Paternal use of SASP has been linked to oligospermia (193). Folic acid supplementation should be started, and SASP should be discontinued for 3 months in male patients who fail to conceive (180).

**Thalidomide:** Thalidomide is contraindicated during pregnancy and lactation. The use of condoms is recommended as the excretion of thalidomide into the semen has been established during paternal use (194).

**Cyclosporine:** Although cyclosporine is mainly used in rheumatic diseases and transplantation clinics, cyclosporine therapy may also be required in patients with UC. The consensus is that it may be used at the lowest effective dose, at any stages of pregnancy (195). Pregnant patients on cyclosporine should be closely monitored with respect to well-known side effects including diabetes, nephrotoxicity, hypertension, or electrolyte imbalances. Although paternal cyclosporine use has been considered safe, studies on paternal use are insufficient in number and sample size (179).



**Figure 3.** The JAK-STAT signaling pathway. JAK inhibitors are new therapeutic agents which are currently being investigated in clinical trials in IBD. First-generation JAK inhibitors (e.g., tofacitinib) target multiple JAKs, whereas second-generation JAK inhibitors (e.g., filgotinib) selectively target one JAK (161).

### Use of biologics during pregnancy

TNF- $\alpha$  plays an important role in the implantation and development of the placenta (196). Therefore, hypothetically, TNF blockage may be associated with an increased risk for in-utero developmental abnormalities and abortions. However, an increased prevalence of developmental abnormalities or abortions has not been observed in pregnant patients who had been accidentally exposed to anti-TNF agents (173,180,197).

TNF inhibitors with immunoglobulin structure begin to cross the placenta increasingly by the end of the second trimester. Detectable levels of these medications in the blood of infants until 6 or 7 months after the delivery have raised questions about the administration of live vaccines and developmental disorders of the immune system (198,199). Among anti-TNF agents, only certolizumab pegol may be used throughout the entire pregnancy owing to its low placental transfer rate due to its structural characteristics (198). However, it is recommended to discontinue other anti-TNFs approximately 24-26 weeks of gestation (199). Some authors recommend discontinuing infliximab in week 16 of pregnancy due to hypothetically increased risk for infections in the newborn (180).

On the other hand, no consensus has been established regarding the way to follow in case of active disease or high

risk of disease activation. Any IBD activation which may occur following the discontinuation of anti-TNF therapy is a major risk factor for both mother and baby (200). Furthermore, no association has been demonstrated between the use of anti-TNF agents throughout the entire pregnancy and increased prevalence of malformations, and postpartum long-term safety of these agents has been established (201,202). Therefore, we believe that anti-TNF agents should not be discontinued in the last trimester of the pregnancy in patients at high risk of disease activation and in those who exhibit a partial response to anti-TNF therapy, while necessary measures should be taken after the delivery. Clinicians should also be careful about infectious side effects under anti-TNF treatment in pregnancy (202).

If anti-TNF agents are considered in the management of CD, patients who are planning to conceive may be started on certolizumab due to its better safety profile. In the event that another anti-TNF agent (infliximab or adalimumab) is used and cannot be discontinued in the third trimester due to active disease or high activation risk, then live vaccines should be deferred >7 months of age in infants born to these mothers. Other vaccines can be timely administered, and normal immune responses have been obtained to these vaccines (203,204).

There are limited data on the use of either ustekinumab or VDZ during pregnancy. Fetal toxicity has not been observed in animal studies. Both medications are allocated to category B by the FDA. If necessary, these medications can be used after the assessment of the benefit/risk balance (205,206). Long-term prediction for these medications is that they will be used in a similar way to anti-TNFs.

### **The use of biologics during lactation**

Anti-TNFs may be used during lactation. All biologics are excreted into human milk in very small amounts (207,208). In addition, biologics may be partially degraded in the stomach due to their protein structure. An increased risk for infections has not been observed in infants breastfed by mothers exposed to anti-TNF (197,201,202). Cessation of lactation is not recommended in patients who are on/are started on an anti-TNF agent; however, current information and recommendations should be followed. There are reports indicating that VDZ is excreted into human milk in small amounts; however, detailed data on the effects of the amount excreted into milk are not available yet (208). Further data are needed on the safety of ustekinumab and VDZ during lactation.

- Anti-TNF agents should be discontinued by the end of the second trimester in patients who are in remission and at low risk for disease activation.
- Certolizumab pegol crosses the placenta in negligi-

ble amounts due to its distinct structure and may be used at any stages of pregnancy.

- Certolizumab may be preferred in patients who are planning to conceive and who will be treated with an anti-TNF agent.
- Live vaccines should be deferred >1 year of age in infants born to mothers exposed to an anti-TNF agent other than certolizumab throughout the entire pregnancy due to disease activation or a high risk for activation.
- Biologics are excreted into human milk in very small amounts.
- Cessation of lactation is not recommended in mothers who are on/are started on an anti-TNF agent; however, current information and recommendations on such use should be followed.

Summary of recommendations regarding the use of medications during pregnancy and lactation is given in Table 8.

### **Use of conventional therapy and biologics in patients with malignancies**

Long-term follow-up of transplant patients has demonstrated that immunosuppressants might contribute to the development of malignancies and the risk for malignancies might increase with the duration and combination of immunosuppression (209). The associations between TPs and non-melanoma skin cancers and lymphoma have been established (210,211). However, a number of clinical studies with anti-TNFs have failed to demonstrate an increased risk for cancers. Although MTX have not been investigated as extensively as these medications, the increase in the risk for cancers is not as high as with TPs, and this is the reason why MTX has been the treatment of choice in the management of IBD during the last 4-5 years for patients under the age of 30 years and over the age of 65 years (211).

After the introduction of anti-TNF agents in daily practice, the important role of TNF in inflammation and its ability to kill a number of cancer cells in vitro and animal studies have raised questions about the potential ability of anti-TNF agents to trigger the development of malignancies (212,213). Rare malignancies in patients exposed to these treatments and even tumor regression following the discontinuation of anti-TNFs have been reported in the literature (214-216).

On the other hand, real-world data have not suggested the expected response to treatment with TNF in a variety of cancer types (217). On the contrary, certain studies suggested that TNF might promote tumor growth in patients with breast, lung, pancreas, or kidney cancer (217-220). In certain clinical and laboratory studies, even conventional or targeted chemotherapy was used in combination with an anti-TNF

**Table 8.** Medication use in the management of IBD during pregnancy and lactation.

Medication	Use during the first trimester	Use during the 2nd and 3rd trimesters	Pregnancy category	Use during lactation	Recommendations
Thiopurines	Allowed	Allowed	D	Allowed	They can be used in low-risk patients with or without dose reduction according to the benefit/risk balance
MTX	Contraindicated	Contraindicated	X	Not recommended	MTX should be discontinued, and folic acid supplementation should be started 3 months before conception. MTX should be immediately discontinued if pregnancy occurs during treatment with MTX, close monitoring and folic acid supplementation are required during pregnancy
Cyclosporine	Allowed	Allowed	C	Allowed	The lowest effective dose should be given
Glucocorticoids	Allowed	Allowed	C	Allowed	It can be used at any stages of pregnancy. There are controversial data on an increased prevalence of cleft lip and palate
5-ASA, sulfasalazine	Allowed	Allowed	B	Allowed	Formulations containing dibutyl phthalate are available abroad. These formulations are not recommended during pregnancy
Thalidomide	Contraindicated	Contraindicated	X	Contraindicated	Major teratogenicity, use of condoms is recommended due to paternal teratogenicity
Anti-TNF	Allowed	Allowed*	B	Allowed	*TNFs other than certolizumab should be discontinued approximately 24 weeks of gestation. Treatment may be continued in patients at high risk of disease activation. In this case, live vaccines should be deferred beyond 7 months of age in infants born to these mothers
Vedolizumab	Limited data	Limited data	B	Limited Data	Vedolizumab can be used with caution if necessary
Ustekinumab	Limited data	Limited data	B	Limited Data	Ustekinumab can be used with caution if necessary
Metronidazole	Allowed**	Allowed	B	Not recommended	**The use of metronidazole >1 week is not recommended throughout the pregnancy and particularly during the first trimester. The excretion of metronidazole into human milk is proportional to plasma concentrations. Temporary cessation of breastfeeding is recommended during treatment with metronidazole.
Ciprofloxacin	Contraindicated	Not recommended	C	Not recommended	Minor musculoskeletal malformations observed in animal studies have not been observed in studies in women exposed to ciprofloxacin during pregnancy. Ciprofloxacin is contraindicated during pregnancy as safer alternatives are available.

agent to optimize anti-tumor activity (221-222). Therefore, it should be known that TNF may exhibit both pro-neoplastic and anti-neoplastic effects.

The assessment of real-world data for anti-TNFs revealed that a slight increase occurred in the risk for the development of melanoma (210). Data on the development of

lymphoma are conflicting (210-211). A recently published study with a large sample size have demonstrated that monotherapy with anti-TNFs might slightly increase the risk for the development of lymphoma. The risk for the development of lymphoma has been found to be higher with combination therapy with an anti-TNF agent and TP than with treatment with TP or an anti-TNF alone (223). Results for non-melanoma skin cancers are conflicting.

No evidence of an increased risk for malignancy has been detected in phase studies and real-world data of VDZ and ustekinumab. Data from a large population of patients with psoriasis did not reveal any increased risk for malignancy (102). Hypothetically, VDZ may be safe regarding extraintestinal malignancies due to GIS selectivity; however, real-world data on the use of VDZ are limited.

Studies on cancer development with anti-TNFs cover a period of 15 years at most. Longer term outcomes of the exposure to biologics are not known yet. Although larger studies predict that either anti-TNF agents (224,225) or immunomodulatory agents (225) do not increase the risk for recurrence or a secondary malignancy in patients with a known malignancy, immunosuppressives should not be given, unless there is a clear-cut indication. In general, the management plan should start with the modality and drug class with the least malignancy potential (surgery, 5-ASA, SASP, and oral budesonide). The consensus on the initiation of immunosuppressive therapy in patients with cancer is to wait 2 years after treatment, whereas this period should be at least 5 years in cancers which are known to recur at high rates under immunosuppressive treatment including skin, bladder, and kidney cancers; sarcoma; leukemia; or myeloma (209,210). We believe that the length of this period may be adjusted according to the risk/benefit balance based on the shared decision and approval of the patient and corresponding specialists (oncologists, hematologists, and dermatologists) in patients with active disease experiencing a significant decrease in the quality of life. Anti-TNFs, steroids, and MTX may be used without waiting, if indicated, in patients who are at risk for developing life-threatening short-term and long-term complications (toxic megacolon, short bowel syndrome, and subileus).

Furthermore, one should keep in mind that targeted therapies which have been recently introduced in oncology practice may also induce the activation of IBD or IBD-like colitis (226). This issue is likely to become a growing challenge for gastroenterologists in the future.

Rules for the use of conventional therapy and biologics in patients with malignancies are as follows:

- It still remains unknown how anti-TNFs will act in a given malignancy. Anti-TNFs and other immunosup-

pressive agents should be discontinued in patients with newly diagnosed malignancy.

- Anti-TNF agents should be avoided in patients with known melanoma/history of melanoma.
- Case-based assessment is required in the management of active IBD.
- Hypothetically, VDZ may be safe in patients with extraintestinal malignancy; however, real-world data are limited.
- Malignancy potential of ustekinumab has not been observed in limited series; however, there are limited data from patients with a history of malignancy.
- Surgery may be the treatment of choice in patients with short segment involvement.
- When colitis is active, biologics may be used in patients with terminal-stage malignancy, as the primary objective is to improve the quality of life and pain relief.

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