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Original Article

Iranian Consensus Guideline for Pharmacotherapy with Biologics and Small Molecules Drugs in Adults with Inflammatory Bowel Diseases

Niloofar Khoshnam-Rad[1], Homayoon Vahedi[2], Anahita Sadeghi[2], Mansoor Rastegarpanah[1], Soha Namazi[1], Amir Anushiravani[2], Ali Reza Sima[3], Shabnam Shahrokh[4], Sudabeh Alatab[2*], Reza Malekzadeh[2]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[2]Digestive Disease Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[3]Sasan Alborz Biomedical Research Center, Masoud Gastroenterology and Hepatology Center, Tehran, Iran
[4]Basic and Molecular Epidemiology of Gastrointestinal Disorders Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: Pharmacotherapy with biologics and small molecules, as the more effective therapies for moderate to severe ulcerative colitis (UC) and Crohn's disease (CD), is complex. Choosing the best methods for their utilization in order to induce and maintain remission are critical for practicing gastroenterologists. We aimed to develop an Iranian consensus on the management of inflammatory bowel disease (IBD) patients with biologics and small molecules.

Methods: A Delphi consensus was undertaken by experts who performed a literature summary and voting process. Quality of evidence was assessed using the Grading and Recommendations Assessment, Development, and Evaluation; and an additional risk of bias-protocol.

Results: Following an extensive search of the literature, 219 studies were used to determine the quality of the evidence. After three rounds of voting, consensus (defined as ≥ 80% agreement) was reached for 87 statements.

Conclusion: We considered different aspects of pharmacotherapy in this consensus. This guideline, along with clinical judgment, can be used to optimize management of IBD patients.

Keywords: Consensus guideline, Biologic drugs, Small therapeutic molecules, Pharmacotherapy

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Introduction

Ulcerative colitis (UC) and Crohn's disease (CD), the two main forms of inflammatory bowel diseases (IBDs), are chronic immune-inflammatory disorders of the gastrointestinal tract. Following the westernization of lifestyle, IBD is now a global disease.[1] Although the incidence rate of IBD is stabilizing in some western countries, the incidence rate is increasing in non-western countries. A nationwide report in Iran showed a rising incidence and prevalence trend of both UC and CD.[2] IBD treatment is transforming with expanding pharmacological options (non-conventional therapies: biologics and small molecules) targeting different pathways of the immune system with higher efficacy.[3] To optimize the use of biologics and small molecules in the treatment of moderate to severe IBD, multiple factors that influence outcomes should be considered.[4]

We aimed to develop an Iranian consensus on the management of IBD with biologics and small molecules. The results of this consensus offer the clinician a guidance in managing the pharmacotherapy of IBD patients to improve outcomes.

Materials and Methods

We initiated a Delphi process to develop consensus statements on different aspects of biologics and small molecule usage in adult patients with IBD. The principal steps in the process were: (1) selection of a working group of ten members; (2) drafting of statements to evaluate the current knowledge on the drugs in IBD; (3) systematic literature review for identifying evidence to support each statement; (4) grading the strength of recommendations, and (5) two rounds of repeated voting and voting discussion for reaching the consensus.

Members were experts in gastroenterology, general practice, and pharmacotherapy. All members submitted a conflict of interest statement before the voting sessions.

Three- core group members (N.K, S.A, H.V) first formulated a series of specific questions using the Population, Intervention, Comparator, Outcomes

*Corresponding Author: Sudabeh Alatab, Email: sudabehalatab@yahoo.com

(PICO) system, which were deemed to be relevant to optimize therapy with biologics and small molecules. The current available biologic drugs in our country include infliximab, and adalimumab. Tofacitinib is also available as a small molecule in Iran. We have understood that drugs of ozanimod, ustekinumab and vedolizumab may enter the pharmaceutical market of Iran shortly, therefore we assumed that it would be appropriate to include these drugs in our protocol as well.

The existing guidelines were reviewed to determine questions and challenges. Medical databases, including Medline, Embase, and Cochrane Central, were systemically reviewed from inception to January 25, 2022. The search phrases used in this study are provided in Supplementary file 1 (Table S1).

N.K, S.A, and H.V drafted and finalized a list of statements covering the majority of pharmacotherapy aspects in IBD. Finally, 94 clinical statements were extracted. Evidence quality is defined as A (high), B (moderate), C (low), and D (very low). If the quality of evidence in the statement could not be determined, it was defined as a good practice recommendation. The decision-making method for determining the quality of evidence is shown in Figure 1. Bias risk was determined based on an assessment of randomization, concealment, intention to treat, blinding, follow-up completion, early cessation of study due to patient benefit, or reporting of selected outcomes. The strength of each recommendation was graded either as "strong" meaning the desirable effects of an intervention outweigh the undesirable effects or vice versa; or as "weak" meaning the balance is less determined. The quality of evidence, patients' preferences, the balance between desirable and undesirable effects, and cost-effectiveness also were considered.

The literature review, related evidence, and references were emailed to all members. The finalized graded list of 94 statements was evaluated in a first voting round by all members in the last quarter of 2021. Participants were blinded to the votes of other participants. Participants gave feedback on the clarity of statements and made suggestions for adapting or splitting the statements or adding additional points on a given topic. Members also ranked clinical importance of each outcome on a scale of 1 to 9, based on GRADE definitions; scores of 7–9 suggested a critical outcome; scores of 4–6 indicated an important outcome; and scores of 1–3 indicated an outcome of limited importance for decision making.

A final voting round was conducted by early 2022 for finalizing the statements that were under debate.

The consensus was defined as when ≥ 80% of the voting group agreed with a statement. After the last voting round, manuscript was drafted and circulated for approval by expert group members.

The references cited in this article are only a selection of the studies reviewed in each area.

Results

Following an extensive search of the literature, 219 studies were used to determine the quality of evidence. We categorized the statements into 13 groups (A to M) addressing different aspects of pharmacotherapy. After three rounds of voting, consensus was reached for 87 statements. In the following sections, the recommendations and a brief rational for each statement is provided. Also a summary of recommendations is presented in Table 1.

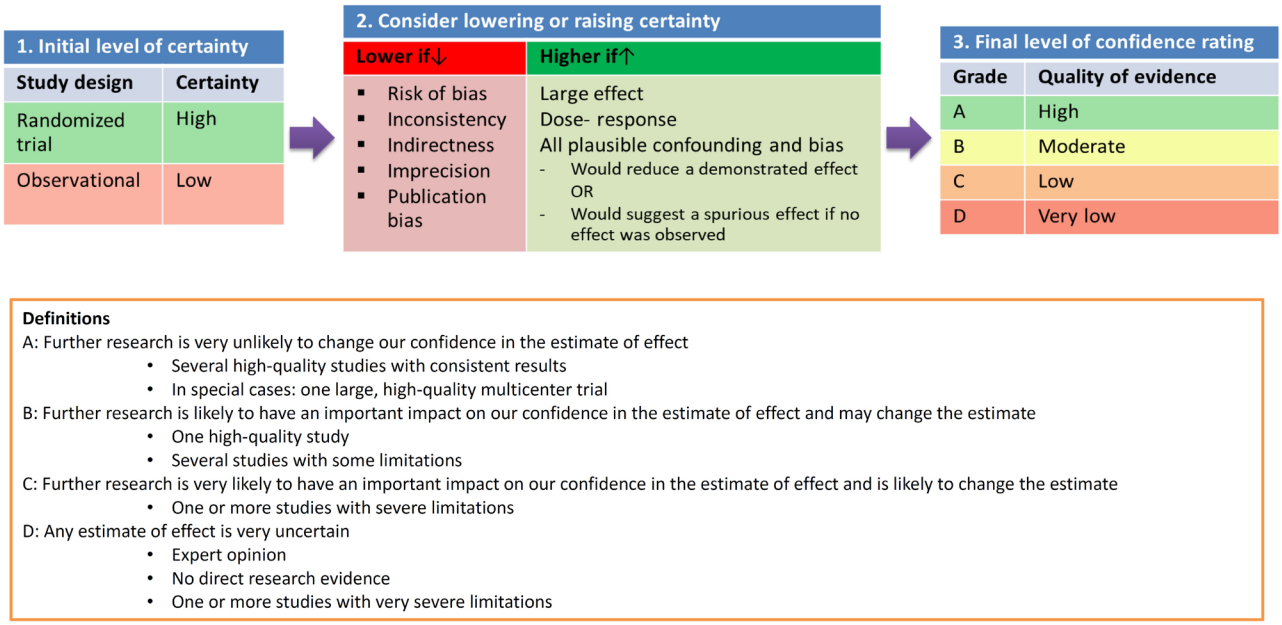

Figure 1. Decision-making method for determining the quality of evidence

Table 1. Summary of recommendations

No.	COR	LOE	Agreement	Statement
A. Biologic drugs indication and place in therapy of Crohn's disease				
A-1	Strong	B	100	We recommend that CD patients refractory to optimized immunomodulator maintenance therapy or steroid-refractory patients should be considered for biological therapy. The choice between anti-TNF drugs (IFX, ADA), ustekinumab, and vedolizumab should be made on an individual basis considering patient preference and adherence, availability, cost, safety data, and pharmacokinetic profile of the drug
A-2	Strong	A	100	We recommend that combination therapy of IFX and azathioprine should be used, as it is more effective than monotherapy and reduces immunogenicity.
	Weak	B	100	We suggest that combination therapy of IFX with methotrexate instead of azathioprine in cases of contraindication or intolerance.
A-3	Strong	C	96	We recommend combination therapy of anti-TNF drugs and immunomodulators for patients younger than 30 years old or older than 60 years old for at least 6-12 months. This combination is specifically critical in patients who are receiving IFX and is less important with non-anti-TNF biologics.
A-4	Weak	D	89	We suggest 1-1.25 mg/kg of azathioprine in combination therapy for reducing the immunogenicity of biologics.
A-5	Strong	A	100	We recommend that patients with moderate to severely active uncomplicated luminal CD should be initially treated with systemic corticosteroids
	Weak	C	90	We suggest that in case of extensive disease or patients with at least two other poor prognostic factors, early introduction of biological therapy (earlier than 18 months after diagnosis) should be considered.
A-6	Strong	A	100	We recommend that ustekinumab or vedolizumab should be used in CD patients with anti-TNF-α failure. The use of these drugs in biologics-naïve patients should be individualized.
A-7	Strong	B (IFX) C (ADA)	100	We recommend that IFX and ADA are effective in the treatment of perianal fistula and should be considered.
	Weak	D	80	If anti-TNFs are not effective or tolerated, ustekinumab may be considered to treat fistula.
B-1	Strong	A	100	We recommend that anti-TNF drugs (IFX and ADA) could be prescribed as induction and maintenance therapy in patients with moderate to severe UC, both in biologics-naïve patients and after the failure of conventional therapy.
B-2	Strong	A	100	We recommend that ustekinumab or vedolizumab should be used in UC patients with anti-TNF failure. The use of these drugs in biologics-naïve patients should be individualized.
B-3	Strong	D	85	We recommend early treatment with biologic in moderate to severe UC with poor prognosis factors.
B-4	Strong	C	90	IFX is more effective than other biologics in moderate to severe UC and should be prescribed in combination with an immunomodulator.
B-5	Strong	C	100	We suggest treatment with IFX rather than cyclosporine in steroid-refractory ASUC.
	Weak	C	89	In ASUC patients who respond well to IFX induction, maintenance therapy should be continued with IFX.
B-6	Strong	C	90	We recommend accelerated IFX induction (10 mg/kg) in ASUC patients with no response to standard dose of IFX.
B-7	Strong	C	100	We recommend against combination therapy with IFX and cyclosporine in ASUC.
B-8	Strong	B	90	We recommend tofacitinib in moderate to severe UC patients with biologic failure history or in cases of intolerance or contraindication to biologic drugs.
B-9	Strong	C	100	We recommend that ozanimod can be considered in moderate to severe UC.
B-10	Weak	D	90	We suggest that in cases of UC treatment failure with IFX, ustekinumab is more effective than ADA or vedolizumab; however, the choice between these drugs should be individualized.
C. Considerations regarding prescription of drugs				
C-1	Good practice		100	Biologic drugs should always be prescribed with an appropriate dose by a qualified physician. Biologics should be administrated according to the protocol to reduce infusion-related adverse effects.
C-2	Good practice		100	Tofacitinib dose should be adjusted in renal dysfunction and moderate to severe hepatic dysfunction. It has not been studied in patients with severe hepatic impairment or patients with hepatitis B or hepatitis C viruses, so it is not recommended in this population.
D. TDM				
D-1	Strong	C	100	We recommend that in cases of secondary loss of response, anti-TNF drug and antibody levels should be measured by a validated method, and dose adjustment or drug switch should be considered based on the results.
D-2	Weak	D	90	We suggest measuring trough and antibody levels at 14th week of therapy with IFX and 12th week of therapy with ADA. In patients with undesirable initial response, levels may be measured 2-4 weeks after induction.
D-3	Weak	D	90	We suggest higher anti-TNF levels in patients with active disease or perianal involvement.
D-4	Weak	D	90	We suggest against the addition of immunomodulators to ustekinumab or vedolizumab due to decreasing the immunogenicity and antibody production of these biologics in this setting.
D-5	Weak	D	90	We suggest that TDM of anti-TNFs is also beneficial in the following occasions: when drug holiday is considered, when immunomodulator discontinuation is necessary (due to adverse effects), when non-compliance is suspected (any cause), in obese patients, and in patients without early response.

Table 1. Continued.

No.	COR	LOE	Agreement	Statement
D-6	Weak	D	90	We suggest re-induction of vedolizumab in patients who have a partial primary response to induction dose. In cases of partial response to maintenance doses, a shorter interval may be considered.
D-7	Weak	D	100	We suggest a shorter interval of ustekinumab administration for selected patients (history of anti-TNF failure, a higher burden of inflammation, heavier than 100 kg) when ustekinumab trough level is lower than therapeutic range. In patients who have a partial primary response or in cases of secondary loss of response to the drug, re-administration of the induction dose may be considered.
E. Contraindications and monitoring parameters				
E-1	Strong	D	90	We recommend evaluating CBC, LFT, and screening for latent tuberculosis, HIV status, HBV, HCV (especially when suspecting acute hepatitis C), and VZV (if no documented history of chickenpox, shingles, or varicella vaccination), before starting biologic drugs unless screened already at the time of diagnosis.
E-2	Strong	D	90	We recommend against prescribing anti-TNFs in patients with moderate to severe heart failure (NYHHA class III and IV) and demyelinating disease.
E-3	Strong	D	100	We recommend against prescribing vedolizumab in patients with PML history. Although the risk is very low with vedolizumab compared to other integrin receptor antagonists, patients should be monitored for and advised to report any neurological symptoms.
E-4	Weak	C	100	We recommend against prescribing biologic drugs, tofacitinib, and ozanimod in patients with sepsis, severe acute infections, active TB, and opportunistic infections, including *Clostridium difficile*.
E-5	Strong	C	100	We recommend annual TB screening, periodic monitoring of CBC and LFT, and periodic evaluation of inflammatory markers (ESR, CRP, fecal calprotectin) in patients receiving biologics or tofacitinib.
E-6	Strong	D	100	We recommend evaluating CBC, LFT, lipid panel, pregnancy test, and screening for latent tuberculosis, HIV status, HBV, HCV, and VZV (if no documented history of chickenpox, shingles, or varicella vaccination), before starting tofacitinib.
E-7	Strong	C	100	We recommend periodic monitoring of CBC with differential, LFT, lipid profile in patients receiving tofacitinib.
	Strong	D	100	Patients should be monitored for and advised to report any symptoms related to gastrointestinal perforation, diverticulitis, thrombosis, and other cardiovascular events.
E-8	Strong	D	100	We recommend CBC, LFT, ophthalmologic exam in patients with a history of uveitis or macular edema, and test for antibodies to VZV in patients without a health care professional–confirmed history of varicella (chickenpox, shingles) or without documentation of a full course of vaccination against VZV before starting ozanimod.
E-9	Weak	D	100	We suggest against prescribing ozanimod in patients with Myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or class III or IV heart failure in the last 6 months; Mobitz type II, second- or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial block, unless the patient has a functioning pacemaker; severe untreated sleep apnea, and those patients who concomitantly use a monoamine oxidase inhibitor.
F. Adverse effects (non-infections and non-malignancy)				
F-1	Strong	D	100	We recommend that anti-TNFs associated adverse effects (hematological, dermatological, autoimmune, cardiac, and neurological) should be managed based on the severity of the reaction. Involvement of the multidisciplinary team may be necessary to explore other treatment options and minimize the adverse effects.
F-2	Weak	D	90	We suggest evaluation of neurologic symptoms in patients receiving ustekinumab to identify cases of PRES and discontinue the drug in suspected cases.
F-3	Strong	D	100	We recommend discontinuation of vedolizumab when suspecting PML and never re-challenge it.
F-4	Strong	D	100	We recommend discontinuation or decreasing the dose of tofacitinib in cases of hepatotoxicity (transaminase elevation to more than 3 × ULN).
F-5	Strong	D	100	We recommend discontinuation of tofacitinib when suspecting gastrointestinal perforation and never re-challenge it.
G. Infections				
G-1	Strong	D	100	We recommend hepatitis A vaccination for sero-negative high risk patients based on risk factors.
G-2	Strong	D	90	We recommend vaccination against hepatitis B in seronegative patients and testing the anti-HBs antibody level 1-2 months after complete vaccination. If the level does not reach the desired level (>10 IU/mL), re-vaccination should be considered.
G-3	Strong	D	100	We recommend treatment with tenofovir for HBsAg+patients for at least one week to 1 month before starting immunosuppressive drugs. Tenofovir should be continued for one year after stopping immunosuppressives. For HBsAg- and Anti-HBc+patients with prior anti-HBV therapy history, HBV prophylaxis is not necessary. In patients without the prior antiviral therapy history with moderate risk of reactivation, pre-emptive approach can be considered.
G-4	Weak	D	100	We suggest against starting biologics in patients with acute hepatitis C infection. In chronic cases of hepatitis C, direct acting agents can be started simultaneously with immunosuppression, but close monitoring of liver function should be considered.
G-5	Strong	C	100	We recommend HPV vaccination for young females and males. The HPV vaccines are not contraindicated in immunosuppressed patients.
G-6	Strong	C	100	We recommend annual influenza vaccination for all patients on immunosuppressive therapy, as they are at enhanced risk of severe influenza infection.

Table 1. Continued.

No.	COR	LOE	Agreement	Statement
G-7	Strong	D	100	We recommend induction therapy with anti-TNF in patients with ASUC and CMV colitis, rapid tapering of corticosteroids, and delaying the azathioprine until completing the antiviral course.
G-8	Strong	D	100	We recommend against serologic testing for HSV. In patients with frequent HSV recurrence, suppressive antiviral treatment should be considered.
G-9	Strong	D	90	We recommend RZV for all patients (except for patients with documented vaccination or history of varicella) with IBD, especially those on immunosuppressive therapy. If RZV is not available, a ZVL can be used in immunocompetent patients with IBD and aged ≥ 50 years or low-dose immunosuppression.
G-10	Strong	D	90	We suggest against routine serologic tests for EBV unless for patients who want to start thiopurines. Use of thiopurines in EBV-IgG negative patients should be avoided.
G-11	Strong	D	90	We recommend treating IBD patients in time of COVID-19 pandemic should be similar to before the pandemic. In severe acute cases, stopping immunosuppressors may be considered.
G-12	Good practice		100	In symptomatic PCR-positive COVID-19 patients, starting biologics should be delayed for three days after improvement of symptoms.
G-13	Strong	C	100	We recommend screening for latent tuberculosis infection before immunosuppression and consider re-screening patients who previously exposed to biologics and JAK inhibitors before switching drugs.
G-14	Strong	D	100	We recommend that active TB infection should be treated for at least 2 months before starting biologic or small molecule therapy.
G-15	Strong	D	100	We recommend that for patients with latent TB infection, chemoprophylaxis should be commenced at least four weeks prior to starting biologics and tofacitinib, except in cases of significant clinical urgency and with specialist advice.
G-16	Strong	D	100	Treatment of bacterial infections is usually similar to healthy population, but the duration of therapy should be longer. In septic patients, moderate to severe immunosuppression should be held until the improvement of acute symptoms.
G-17	Strong	D	100	We recommend Pneumococcal vaccination for all patients with IBD.
G-18	Weak	D	90	We suggest standard PJP prophylaxis with co-trimoxazole for IBD patients who are under treatment with three immunosuppressor agents (steroid, methotrexate, azathioprine, biologics). For patients under treatment with two immunosuppressors, especially when one agent is a calcineurin inhibitor, PJP prophylaxis may be considered.
G-19	Weak	D	90	We recommend against the administration of live vaccines in patients with IBD receiving immunosuppressive therapy. It is recommended to wait for at least 1–4 months (based on the half-life of the immunosuppressor) after the termination of immunosuppressive therapy before administration of a live vaccine and wait for at least one month after live vaccine administration for starting immunosuppressors.
H. Malignancy				
H-1	Weak	D	80	We suggest withholding anti-TNF drugs and thiopurines in patients with IBD who are diagnosed with cancer, if IBD is controlled. In cases of active cancer and uncontrolled IBD, continuing or starting of immunomodulators and biologics can be considered.
H-2	Weak	D	80	We suggest that after the cure of cancer, restarting of anti-TNFs should be considered based on the recurrence rate of cancer. Treatment with drugs with low risk for cancer (ustekinumab and vedolizumab) is preferred.
I. Extra-intestinal manifestations				
I-1	Strong	B	100	We recommend that symptoms of IBD-associated arthropathies should be managed with control of intestinal inflammation, physiotherapy, and simple analgesics. If spondyloarthritis cannot be controlled with these measures, sulfasalazine, methotrexate, anti-TNFs, or tofacitinib may be considered.
I-2	Strong	C	100	We recommend the control of intestinal inflammation in IBD patients who develop erythema nodosum. Anti-TNFs may be considered in refractory or relapsing cases.
I-3	Strong	D	90	We recommend that in IBD patients with pyoderma gangrenosum who fail therapy with steroids, anti-TNFs may be considered.
I-4	Good practice		100	Most cases of anti-TNFs associated dermatological adverse effects can be managed with topical agents, and discontinuation of anti-TNFs is not required. Adding methotrexate or stopping anti-TNF may be considered in refractory cases.
I-5	Strong	D	90	We recommend that uveitis may be controlled with anti-TNFs with the consult of ophthalmologists. Uveitis could also be a paradoxical effect in association with anti-TNFs and should be discontinued in these cases.
I-6	Strong	D	100	We recommend against vedolizumab for IBD patients with EIM. If a patient on vedolizumab therapy develops EIM, adding an effective agent or changing the vedolizumab may be considered.
J. Special populations				
J-1	Strong	D	90	We recommend that for elderly patients with IBD, vedolizumab and ustekinumab are considered preferred options, and tofacitinib should not be chosen in this population unless no other option is effective or tolerable.
J-2	Weak	D	90	We suggest that in obese patients, IFX with TDM is a good choice, as it administered on weight-based dosing. ADA with standard dose and TDM should be considered, and increasing the dose of ADA may be needed.
J-3	Weak	D	90	We suggest that in obese patients, ustekinumab, vedolizumab, and tofacitinib should be administered with standard dose. Close monitoring of response and adjusting the dose may be considered.

Table 1. Continued.

No.	COR	LOE	Agreement	Statement
J-4	Weak	D	80	We suggest that anti-TNF drugs can be continued during pregnancy. TDM before pregnancy is helpful for adjusting the dose to decrease the risk of fetus exposure to inappropriate supra-therapeutic levels. Repeating TDM during pregnancy is not required, unless there are other reasons for TDM.
J-5	Weak	D	90	We suggest that in cases of anti-TNFs discontinuation during pregnancy, it can be restarted 24 hours after natural delivery or 48 hours after cesarean section.
J-6	Weak	D	80	We suggest in patients that discontinuation of vedolizumab or ustekinumab during pregnancy is not feasible: the last dose of the drug should be administrated 6-10 weeks before the expected date of delivery and restarted 48 hours after delivery.
J-7	Strong	D	90	We recommend against treatment with small molecules in pregnancy and lactation, and these drugs (tofacitinib and ozanimod) should be discontinued before conception.
J-8	Strong	D	90	We recommend that anti-TNF drugs can be used during lactation; the decision to use vedolizumab and ustekinumab should balance the benefit of therapy to the mother and the potential risks to the infant.
J-9	Weak	D	80	We suggest that vaccination with inactivated vaccines for newborns and infants from mothers on immunosuppressive drugs should be similar the other newborns and infants. Vaccination with live vaccines generally should be deferred by one year, and BCG vaccination should be delayed for six months.
K. Switching and discontinuation				
K-1	Weak	D	80	We suggest that when there is a clinical need for rapid drug switching, it can be done immediately; however, when it is possible, 3-5 half-life should be considered as a wash-out period before starting the new drug.
K-2	Weak	D	80	We suggest careful decision for discontinuation of all medication in patients after two years of deep remission and without disease relapsing risk factors. Close monitoring of inflammatory markers and restarting therapy immediately after relapse diagnosis should be considered.
L. Surgery				
L-1	Strong	D	100	We recommend against holding anti-TNFs before IBD-related surgeries. If possible, surgery should be planned 4 weeks after the IFX dose (2 weeks for ADA), and the next dose will be administrated 4 weeks (2 weeks for ADA) after surgery.
L-2	Weak	D	90	We suggest against holding ustekinumab and vedolizumab before IBD-related surgery; however, vedolizumab can be associated with delay in postoperative wound healing.
L3	Weak	D	80	We suggest holding tofacitinib one week before surgery and restarting it 3-5 days after surgery, as it can be associated with infectious and thrombotic adverse effects after surgery.
L-4	Strong	C	100	We recommend against preoperative TDM to decide about the time of surgery.
L-5	Weak	D	100	We suggest that for non-IBD related elective surgery, biologic drugs should be started two weeks after surgery.
M. Combination therapy with biologics				
M-1	Weak	D	100	We suggest that for patients with partial response to one biologic drug, the addition of another biologic from another class or small molecule may be considered. For patients with a history of treatment failure with all approved agents, starting two biologics with different mechanisms may be beneficial.
M-2	Weak	D	100	We suggest adding an anti-TNF drug to another class of biologics in IBD patients with uncontrolled axial spondyloarthritis beneficial.
M-3	Weak	D	100	We suggest adding ustekinumab to treatment in IBD patients with uncontrolled psoriasis.
M-4	Weak	D	100	We suggest adding vedolizumab to another biologic in patients with controlled EIM and uncontrolled intestinal inflammation to control the intestinal inflammation, as vedolizumab is not effective for treating EIM

Abbreviations: ASUC, acute severe ulcerative colitis; ADA, Adalimumab; CD, Crohn's disease; COR, confidence of recommendation; EIM, Extra intestinal manifestations; IBD, inflammatory bowel disease; IFX, infliximab; LOE, level of evidence; TDM, therapeutic drug monitoring; UC, ulcerative colitis; CBC, complete blood count; LFT, liver function tests; PML, progressive multifocal leukoencephalopathy; RZV, recombinant herpes zoster vaccine; ZVL, Zoster vaccine live; PJP, *Pneumocystis jirovecii* pneumonia; VZV, Varicella-Zoster Virus; PRES, posterior reversible encephalopathy syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; EIM, extra-intestinal manifestation.

A- Biologic Drugs Indication and Place in Therapy of Crohn's disease

A-1- We recommend that CD patients refractory to optimized immunomodulator maintenance therapy or steroid-refractory patients should be considered for biological therapy. The choice between anti-TNF drugs (infliximab, adalimumab), ustekinumab, and vedolizumab should be made on an individual basis considering patient's preference and adherence, availability, cost, safety data, and pharmacokinetic profile of drug (GRADE: Strong, B. Agreement: 100%).

Anti–TNF drugs have long been considered as first-line biologics for patients with moderate-to-severe luminal CD, patients with extra-intestinal manifestations (EIMs), or patients with complex perianal fistulas.[5] Available anti-TNF drugs in Iran include infliximab and adalimumab. Infliximab demonstrated definitive benefit in luminal CD in the ACCENT I and II studies.[6] A meta-analysis including the CLASSIC-I, GAIN, and CHARM studies, representing over 700 participants with moderate to severe CD, showed a lower likelihood of failure to induce remission on adalimumab vs. placebo.[7] Ustekinumab, a monoclonal antibody against interleukin-12/23, was approved for the treatment of CD based on UNIT-I, UNIT-II, and UNIT-IM studies.[8] Vedolizumab, a monoclonal antibody against $\alpha_4\beta_7$ integrin, was approved for the treatment of CD based on its ability to induce clinical remission, as shown in the GEMINI-2 study.[9]

A network meta-analysis of these five agents ranked infliximab and adalimumab as the most effective drugs for induction in patients with no previous exposure to anti–TNF agents. Ustekinumab was ranked as the most effective for inducing clinical remission in patients with previous exposure to anti–TNF therapy.[10] Considering patient's preference and adherence, availability, cost, safety data, and pharmacokinetic profile of the drug are necessary for selecting the appropriate therapy.

A-2- We recommend that combination therapy of infliximab and azathioprine should be used, as it is more effective than monotherapy and reduces immunogenicity (GRADE: Strong, A. Agreement: 100%). We suggest that combination therapy of infliximab with methotrexate instead of azathioprine in cases of contraindication or intolerance (GRADE: Weak, B. Agreement: 100%).

A-3- We recommend combination therapy of anti-TNF drugs and immunomodulators for patients younger than 30 years old or older than 60 years old for at least 6-12 months. This combination is specifically critical in patients who are receiving infliximab and is less important with non-anti-TNF biologics (GRADE: Strong, C. Agreement: 96%).

A-4- We suggest 1-1.25 mg/kg of azathioprine in combination therapy for reducing the immunogenicity of biologics (GRADE: Weak, D. Agreement: 89%).

According to the results of trials, to maximize the efficacy of infliximab therapy and reduce treatment failure, combination therapy with an immunomodulator (with stronger evidence for azathioprine than methotrexate) should be considered.[11] There is less clear evidence for benefit of combination therapy of adalimumab with an immunomodulator; however, concomitant immunomodulator therapy reduces immunogenicity and increases trough levels. It may be clinically beneficial for longer-term adalimumab maintenance therapy and should be considered.[12]

Maintaining therapeutic levels of anti-TNF drugs without antibody formation is feasible with lower doses of azathioprine. Therefore, low dose (1-1.25 mg/kg) is preferred for combination to minimize its side effects.[13]

Continuation of immunomodulators beyond six months offered no clear benefit with infliximab, but it was associated with higher median trough levels and lower CRP levels.[14,15] For patients who are at higher risk of adverse effects, a minimum concomitant therapy for 6-12 months should be considered.

A-5- We recommend that patients with moderate to severely active uncomplicated luminal CD should be initially treated with systemic corticosteroids (GRADE: Strong, A); however, we suggest that in case of extensive disease or patients with at least two other poor prognostic factors, early introduction of biological therapy (earlier than 18 months after diagnosis) should be considered (GRADE: Weak, C. Agreement: 90%).

The treatment paradigm of CD has been shifting from a traditional "step-up" toward a "top-down" approach and early intervention treatment strategy.[16] In patients with severe disease courses or with 'high-risk' poor prognostic factors, early (within 18 months of diagnosis) start of biologics may be beneficial. High-risk features include; complex (stricturing or penetrating) disease at presentation, perianal fistulizing complication, age under 40 years at diagnosis, and requirement for steroids for controlling the index flares.[17]

A-6- We recommend that ustekinumab or vedolizumab should be used in CD patients with anti-TNF failure. The use of these drugs in biologics-naïve patients should be individualized (GRADE: Strong, A. Agreement: 100%).

Vedolizumab (an α4β7 integrin antagonist) and ustekinumab (an IL12/23 inhibitor) are now considered not only as second-line but also as first-line biologic drugs besides anti-TNF drugs. Having a good safety profile, these drugs perhaps will be more administered in the near future.[18]

A-7- We recommend that infliximab (GRADE: Strong, B. Agreement: 100%) and adalimumab (GRADE: Strong, C. Agreement: 80%) are effective in the treatment of perianal fistula and should be considered. If anti-TNF drugs are not effective or tolerated, ustekinumab may be considered to treat fistula (GRADE: Weak, D. Agreement: 80%).

A meta-analysis showed that infliximab was effective in inducing and maintaining fistula healing. The ECCO guideline recommends infliximab as the first-line biologic drug for treating complex fistulizing CD.[19] Trials have shown that adalimumab is an effective drug as first-line therapy for anti-TNF-naïve patients and an important treatment choice for infliximab-refractory or -intolerant patients.[20] One meta-analysis of nine trials showed the efficacy of ustekinumab on fistulizing CD.[21]

B- Biologic and Small Molecules Indications and Place in Therapy of Ulcerative Colitis

B-1- We recommend that anti-TNF drugs (infliximab and adalimumab) could be prescribed as induction and maintenance therapy in patients with moderate to severe UC, both in biologics-naïve patients and after the failure of conventional therapy (GRADE: Strong, A. Agreement: 100%).

Several randomized clinical trials compared anti-TNF drugs with placebo in patients with moderately-to-severely active UC who have an inadequate response to or intolerance of conventional therapies. ECCO guideline meta-analysis revealed evidence of efficacy for induction of clinical remission, clinical response, and mucosal healing.[22]

B-2- We recommend ustekinumab or vedolizumab should be used in UC patients with anti-TNF failure. The use of these drugs in biologics-naïve patients should be individualized (GRADE: Strong, A. Agreement: 100%).

Though the overall quality of evidence was low for ustekinumab[23] and vedolizumab,[24] they are viable options for patients with conventional therapy failure or intolerance and in cases of anti-TNF failure.[22]

B-3- We recommend early treatment (less than 2 years) with biologic in moderate to severe UC with poor prognosis factors (GRADE: Strong, D. Agreement: 85%).

Unlike in CD, the optimal time commencing biologic therapy has not been identified in UC. No post-hoc analysis has demonstrated increased efficacy of early introduction of anti-TNF drugs in UC.[22] Poor prognosis factors, including young age at diagnosis, extensive disease, and high inflammatory burden, have been proposed to identify patients who may benefit from early treatment.[25]

B-4- Infliximab is more effective than other biologics in moderate to severe UC and should be prescribed in combination with an immunomodulator (GRADE: Strong, C. Agreement: 90%).

No study directly compared efficacy or safety of anti-TNF drugs. Two network meta-analyses of indirect comparisons concluded that infliximab is superior to adalimumab for induction of clinical remission.[22,26] Like CD, concomitant use of the anti-TNF drugs, especially infliximab, with immunomodulators is superior to infliximab monotherapy and is universally recommended in UC patients.[15]

B-5- We suggest treatment with infliximab rather than cyclosporine in steroid-refractory acute severe ulcerative colitis (ASUC) (GRADE: Strong, C. Agreement: 100%)). In ASUC patients who respond well to infliximab induction, maintenance therapy should be continued with infliximab (GRADE: Weak, C. Agreement: 100%).

B-6- We recommend accelerated infliximab induction (10 mg/kg) in ASUC patients with no response to standard dose of infliximab (GRADE: Strong, C. Agreement 90%).

B-7- We recommend against combination therapy of infliximab and cyclosporine in ASUC (GRADE: Strong, C. Agreement 100%).

Adult patients with ASUC, defined by the modified Truelove and Witts criteria as > 6 bloody stools per day and systemic toxicity with at least one criteria (temperature > 37.8°C, heartbeat > 90 bpm, hemoglobin < 10.5 mg/dL or CRP) > 30 mg/L) should be admitted to the hospital.[27] Cases that cannot be controlled with intravenous corticosteroids after three days should be considered for rescue therapy or surgery. Both infliximab and cyclosporine are effective in ASUC management. Head-to-head comparisons between cyclosporine and infliximab have shown similar efficacy; however, infliximab is more convenient for use and has better tolerability. As sequential therapy with infliximab and cyclosporine can be associated with severe immunosuppression and higher risks for serious adverse events and infections, it is not recommended.[12] Patients treated with infliximab who do not respond adequately to a 5 mg/kg dose after 3–5 days can be treated with a repeat infusion, especially in those with low albumin levels (below 3.5 mg/dL). Some clinicians prescribe a 10 mg/kg dose as salvage therapy at first, but there is insufficient data to demonstrate superior efficacy in comparison to a 5 mg/kg dose regimen.[28] The optimal regimen (5 mg/kg or 10 mg/kg) is still unclear. Accelerated dosing should only be given after colorectal surgical consult, with the agreement that colectomy is not required immediately. The role of drug levels and biomarkers or determining personalized dosing is yet unclear.[12]

B-8- We recommend tofacitinib in moderate to severe UCpatients with biologic failure history or in cases of intolerance or contraindication to biologic drugs (GRADE: Strong, B. Agreement 90%).

FDA has approved tofacitinib[22,29] and upadacitinib[30,31] as alternative agents for adults with moderate to severe UC who have not responded or are intolerant to anti-TNF drugs. Tofacitinib (a JAK inhibitor) has the potential benefits of oral administration and lack of immunogenicity. ECCO guideline's met-analysis revealed efficacy in induction of clinical response and clinical remission and endoscopic response. A meta-analysis of randomized clinical trials on tofacitinib showed similar favorable results for clinical and endoscopic endpoints in both biologic naive patients and those with prior anti-TNF drugs exposure.[32] Oral administration of tofacitinib may be suitable for some patients, as first-line therapy.[22] The decision to start tofacitinib in biologic naive patients should be made based on the patient's preferences, treatment cost and insurance coverage, and harm-benefit analysis.

B-9- We recommend that ozanimod can be considered in moderate to severe UC (GRADE: Strong, C. Agreement 100%).

Ozanimod (an oral sphingosine-1-phosphate receptor modulator) showed efficacy in inducing remission for UC patients compared with placebo. Ozanimod use does not require the previous failure with conventional agents, biologics, or other small molecules.[33] Currently, ozanimod is not in Iran's formulary.

B-10- We suggest that in cases of UC treatment failure with infliximab, ustekinumab is more effective than adalimumab or vedolizumab; however, the choice between these drugs should be individualized (GRADE: Weak, D. Agreement 90%).

An indirect network meta-analysis did not show a statistical difference between ustekinumab and anti-TNF drugs or tofacitinib for clinical and endoscopic responses in patients who were naïve to biologic therapy but suggested a possible benefit of ustekinumab over adalimumab or vedolizumab for patients with previous infliximab exposure.[26]

C- Considerations Regarding Prescription of Drugs

C-1- Biologic drugs should always be prescribed in appropriate dose by a qualified physician. Biologics should be administrated according to the protocol to reduce infusion-related adverse effects (Good Practice recommendation, agreement 100%).

Biologic drugs are relatively safe; however, appropriate dose, administration, monitoring, and management of

hypersensitivities and infusion-related adverse effects should be considered. Appropriate drug desensitization can be performed for patients when there is no other option to control the disease.[34,35]

C-2- Tofacitinib dose should be adjusted in renal dysfunction and moderate to severe hepatic dysfunction. It has not been studied in patients with severe hepatic impairment or patients with hepatitis B or hepatitis C viruses, so it is not recommended in this population (Good Practice recommendation, agreement 100%).

The clearance of tofacitinib is mainly (about 70%) non-renal (hepatic metabolism primarily via cytochrome P450 [CYP] 3A4, with a minor contribution from CYP2C19). While subjects with mild liver dysfunction had similar pharmacokinetic parameters to healthy volunteers, subjects with moderate hepatic impairment had a moderate change in these parameters.[36] Thus, dose adjustment is necessary for moderate to severe hepatic impairment. As tofacitinib was not studied in hepatitis B or hepatitis C infection, it is not recommended for these patients.

A study assessed the impact of renal dysfunction on the disposition of tofacitinib in patients with mild (Cockcroft–Gault creatinine clearance > 50 and ≤ 80 mL/min), moderate (≥ 30 and ≤ 50 mL/min), and severe (< 30 mL/min) renal impairment, and end-stage renal disease patients who required dialysis. This study revealed a change in area under the curve (AUC), so dose reduction is necessary for patients with moderate to severe kidney dysfunction.[37]

Dose reduction to 5 mg twice daily (if taking 10 mg twice daily) or 5 mg daily (if taking 5 mg twice daily) is recommended for patients with eGFR of less than 50 mg/mL or moderate to severe cirrhosis (Child-Paugh B and C).

D- Therapeutic Drug Monitoring (TDM)

D-1- We recommend that in cases of secondary loss of response (LOR), anti-TNF drug and antibody levels should be measured by a validated method, and dose adjustment or drug switch should be considered based on the results (GRADE: Strong, C. Agreement 100%).

D-2- We suggest measuring trough and antibody levels at 14th week of therapy with infliximab and 12th week of therapy with adalimumab. In patients with undesirable initial response, levels may be measured 2-4 weeks after induction (GRADE: Weak, D. Agreement 90%).

Evidence suggests that desirable serum concentrations of anti-TNF drugs in patients with IBD are associated with a better response to treatment, endoscopic healing, and improved quality of life. It also reduced relapse rates, hospitalizations, surgeries, and risk of complications. However, approximately one-third of IBD patients are primary non-responders, meaning that they do not show a response to anti-TNF therapy during the induction phase. Furthermore, 20–40% of initial responders lose response over time (secondary LOR). Strategies for managing LOR to anti-TNF include dose escalation, shortening the dosing interval, adding or switching concomitant immunomodulators, or switching to an alternative drug. These strategies should be guided based on reactive TDM results. Ideally, TDM and treat-to-target management should both be considered to achieve best response.[38]

Proactive TDM can be performed during the induction or post-induction phase or maintenance phase in asymptomatic patients without evidence of active disease. The optimal time point for proactive monitoring is not determined; week 12 for adalimumab and week 14 for infliximab seems reasonable. Earlier monitoring (week 2-4) may be considered in patients with a higher risk of LOR.[39] Management of anti-TNF therapy based on TDM results is presented in Figure 2.

D-3- We suggest higher anti-TNF levels in patients with active disease or perianal involvement (GRADE: Weak, D. Agreement 90%).

In some scenarios, higher or lower trough levels may be appropriate. It appears that higher therapeutic anti-TNF drug trough levels are more appropriate in patients with an overall higher inflammatory burden.[40] There is some evidence that higher anti-TNF levels are associated with perianal fistula healing and fistula closure.[41,42] While the upper limit range is varied in different laboratories, generally the upper limit levels is between 3-8 µg/mL for Infliximab and 5-10 µg/mL for adalimumab.

D-4- We suggest against the addition of immunomodulators for decreasing the immunogenicity of ustekinumab or vedolizumab, as antibody production with these biologics is less likely (GRADE: Weak, D. Agreement 90%).

Combination therapy with a thiopurine or methotrexate and anti-TNF agents is well-established to diminish immunogenicity; however, whether patients with IBD on non-anti-TNF biologics should receive concomitant immunomodulators is controversial. In a recent meta-analysis, no benefit was found for combination therapy of vedolizumab or ustekinumab with an immunomodulator over monotherapy.[43] Thus, immunomodulators should not be started to decrease immunogenicity in patients who receive non-anti-TNF biologic agents.

D-5- We suggest the beneficial of TDM of anti-TNF drugs when drug holiday is considered, when immunomodulator discontinuation is necessary (due to adverse effects), when suspecting non-compliance (any cause), in obese patients, and in patients without early response (GRADE: Weak, D. Agreement 90%).

In addition to TDM in cases of treatment failure, drug and antibody level measurement can be beneficial in some situations. As drug discontinuation or drug holiday could result in relapse and complications, TDM before anti-TNF drug cessation should be considered to stratify the subsequent risk of relapse. Sub-therapeutic or undetectable trough levels are associated with a lack of relapse following anti-TNF drug cessation in carefully selected cohorts, as these patients are no longer dependent

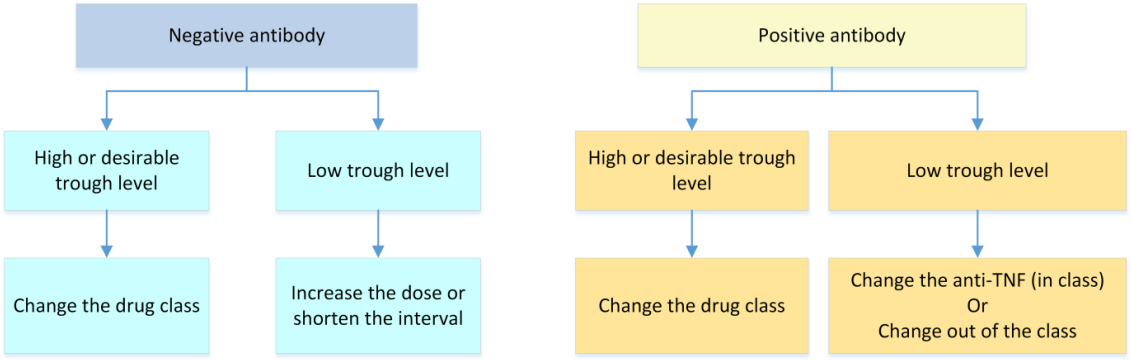

Figure 2. Management of anti-TNF therapy based on TDM results

on anti-TNF drug exposure to maintain remission. Additional predictors for maintaining clinical remission, including the lack of recent corticosteroid use, no prior bowel resections, non-smoking status, female gender, hemoglobin > 14.5 mg/dL, endoscopic mucosal healing, and normalization of inflammatory biomarkers should also be considered before the drug holiday.[44]

Immunomodulators can decrease immunogenicity and have also been shown to increase drug levels, possibly by direct suppression of anti-drug antibody production, decreasing the monoclonal antibody clearance by the reticuloendothelial system, or reducing the inflammatory burden. Immunomodulator discontinuation may lead to lower anti-TNF levels; thus, TDM is reasonable to evaluate the drug and antibody levels.[38] A recent retrospective study showed that immunomodulator withdrawal did not have association with risk of LOR within the following 1–2 years, but an increase in anti-drug antibodies was reported.[15]

As higher body mass index is associated with an increased risk of treatment failure in biologic-treated patients,[45] we suggest TDM in this population to consider dose escalation if necessary.

Early proactive TDM could be beneficial to reach higher therapeutic thresholds which is associated with decreased rate of nonresponse and short-term mucosal healing.[46]

D-6- We suggest re-induction of vedolizumab in patients who have a partial primary response to induction dose. In cases of partial response to maintenance doses, a shorter interval may be considered (GRADE: Weak, D. Agreement 90%).

D-7- We suggest a shorter interval of ustekinumab administration for selected patients (history of anti-TNF failure, higher burden of inflammation, weight higher than 100 kg) when ustekinumab trough level is lower than therapeutic range. In patients who have a partial primary response or in cases of secondary LOR to the drug, re-administration of the induction dose may be considered. (GRADE: Weak, D. Agreement 100%).

TDM for non-anti-TNF biologics was not recommended by the guideline; however, in an expert opinion, reactive TDM for vedolizumab and ustekinumab in patients showing signs of primary non response or secondary LOR is suggested.[38]

Dose optimization by decreasing the interval or IV re-induction can be employed to establish remission and response in patients with partial response to ustekinumab or LOR in maintenance therapy.[47] In patients who weight more than 100 kg, the ustekinumab clearance is about 55% higher than those with a weight of ≤ 100 kg. A history of anti-TNF failure or a higher burden of inflammation is also associated with nonresponse; thus, re-induction may be considered in these patients.[46]

Similar to ustekinumab, limited data demonstrated that vedolizumab dose optimization in patients with low trough levels and secondary LOR improves outcomes. Dose escalation by increasing dosing frequency from eight to every four weeks has been reported to increase rates of clinical remission.[47]

E- Contraindications and Monitoring Parameters

E-1- We recommend evaluating complete blood count (CBC), liver function tests (LFT), and screening for latent tuberculosis, human immunodeficiency virus (HIV) status, Hepatitis B virus (HBV), hepatitis C virus (HCV) (especially when suspecting acute hepatitis C), and Varicella-Zoster Virus (VZV) (if no documented history of chickenpox, shingles, or varicella vaccination), before starting biologic drugs unless patients being already screened at time of diagnosis (GRADE: Strong, D. Agreement 90%).

E-2- We recommend against prescribing anti-TNF drugs in patients with moderate to severe heart failure (NYHHA class III and IV) and demyelinating disease (GRADE: Strong, D. Agreement 90%).

E-3- We recommend against prescribing vedolizumab in patients with progressive multifocal leukoencephalopathy (PML) history. Although the risk is very low with vedolizumab compared to other integrin receptor antagonists, patients should be monitored for and advised to report any neurological symptoms (GRADE: Strong, D. Agreement 100%).

E-4- We recommend against prescribing biologic drugs, tofacitinib, and ozanimod in patients with sepsis, severe acute infections, active tuberculosis, and opportunistic infections, including Clostridium difficile (GRADE: Weak, C. Agreement 100%).

E-5- We recommend annual tuberculosis screening, periodic monitoring of CBC and LFT, and periodic evaluation of inflammatory markers (ESR, CRP, fecal calprotectin) in patients receiving biologics or tofacitinib (GRADE: Strong, C. Agreement 100%).

E-6- We recommend evaluating CBC, LFT, lipid panel, pregnancy test, and screening for latent tuberculosis, HIV status, HBV, HCV, and VZV (if no documented history of chickenpox, shingles, or varicella vaccination), before starting tofacitinib (GRADE: Strong, D. Agreement 100%).

E-7- We recommend periodic monitoring of CBC with differential, LFT, lipid profile in patients receiving tofacitinib (GRADE: Strong, C. Agreement 100%). Patients should be monitored for and advised to report any symptoms related to gastrointestinal perforation, diverticulitis, thrombosis, and other cardiovascular events (GRADE: Strong, D. Agreement 100%).

E-8- We recommend CBC, LFT, and ophthalmologic exam in patients with a history of uveitis or macular edema, and test for antibodies to VZV in patients without a health care professional–confirmed history of varicella (chickenpox, shingles) or without documentation of a full course of vaccination against VZV before starting ozanimod (GRADE: Strong D. Agreement 100%).

E-9- We suggest against prescribing ozanimod in patients with myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or class III or IV heart failure in the last 6 months; Mobitz type II, second- or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial block, unless the patient has a functioning pacemaker; severe untreated sleep apnea, and those patients who concomitantly use a monoamine oxidase inhibitor (GRADE: Weak D. Agreement 100%).

The approach to drug toxicities monitoring and contraindications are similar for all agents, although disease-specific concerns should also be considered. The contraindications to anti-TNF drugs are the same as those for use in other diseases, such as rheumatoid arthritis, and briefly include active infections, latent or untreated tuberculosis, demyelinating disease, and moderate to severe heart failure. Thus, before starting these drugs, appropriate tests should be ordered. Infection-related screenings are discussed in section G. Other monitoring parameters, including CBC and LFT, should be assessed periodically.[48] National Institute for Health and Care Excellence (NICE) technology appraisals guidance for biological therapies in IBD recommends an annual review of patients on biologics (infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab). Although evidence to support this recommendation is scarce, it is reasonable to assess the safety and efficacy of long-term treatment.[49]

Based on current data, vedolizumab and ustekinumab are relatively safe medications. Natalizumab (an anti-α (4)-integrin antibody) treatment is associated with the risk of PML. One case of PML in a vedolizumab -treated patient with multiple risk factors (e.g., HIV infection with a CD4 count of 300 cells/mm3 and prior and concomitant immunosuppression) has been reported in the post-marketing reports. Although it is unlikely, the risk of PML cannot be ruled out. Monitoring patients for any new or worsening neurological signs or symptoms should be considered. Vedolizumab should not be administrated for patients with a history of PML.[50]

Patients who are treated with JAK inhibitors should be monitored for signs of infections (such as herpes zoster and tuberculosis), new gastrointestinal symptoms suggestive of diverticulitis or gastrointestinal perforation, and signs and symptoms of thrombosis or cardiovascular disease in high-risk patients. Periodic laboratory monitoring after initial assessment includes CBC, LFT, and lipid profile.[51]

Data regarding ozanimod safety in UC is scant; however, trials in multiple sclerosis patients have shown a good safety profile. Ozanimod is contraindicated in patients with myocardial infarction, unstable angina, stroke, transient ischemic attack, or heart failure in the previous six months. Additional contraindications include, patients with Mobitz type II second- or third-degree atrioventricular (AV) block, sick sinus syndrome, or sinoatrial block (unless the patient has a functioning pacemaker), intense untreated sleep apnea, and for those taking a monoamine oxidase inhibitors.[33] Prior to starting ozanimod, patients should be assessed with a CBC, LFT, cardiac evaluation, and ophthalmic evaluation for patients with a history of uveitis or macular edema. Concomitant medications should be reviewed for potential additive immunosuppressant effects and drugs that could decrease the heart rate or affect AV conduction. Patients without a history of confirmed chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV, and seronegative patients should have VZV vaccination.[52]

F- Adverse Effects (Non-infections and Non-malignancy)

F-1- We recommend that anti-TNF drugs associated adverse effects (hematological, dermatological, autoimmune, cardiac, and neurological) should be managed based on severity of reactions. Involvement of multidisciplinary team may be necessary to explore other treatment options and minimize the adverse effects. (GRADE: Strong D. Agreement 100%).

Anti-TNF drugs associated hematological adverse effects include neutropenia, thrombocytopenia, and anemia. Based on severity of the reactions, appropriate measures, including close monitoring, drug discontinuation, supportive care, and pharmacological treatments, should be considered.[48]

Besides skin malignancies, anti-TNF drugs can cause a range of dermatological disorders including local skin irritation, increased skin infection rates, psoriasis, eczema, acne, and alopecia. Some other less commonly reported dermatological complications include erythema nodosum, granuloma annulare, and interstitial granulomatous

dermatitis. Although some of these complications can be EIMs of disease, temporal association with anti-TNF therapy can help in differentiating disease-related from drug-related complications.[53,54] Psoriasis can be treated clinically with topical agents and without cessation of anti-TNF in milder cases; however, anti-TNF discontinuation may be necessary in more severe cases. Switching to another anti-TNF agent can be associated with recurrence of psoriasis in most cases (52%). Ustekinumab is effective in psoriasis treatment. Although paradoxical worsening of psoriasis with ustekinumab has been rarely reported, it is not directly causing drug-induced psoriasis and can be considered in this situation.[54]

Although the data are mixed, anti- TNF drugs may be associated with heart failure (HF). Concern about this adverse effect arises from trials of anti- TNF drugs and early post-marketing surveillance. Based on current evidence, patients with symptomatic HF should be treated with treatment strategies other than anti- TNF drugs. If patients develop HF while on anti- TNF drugs, this drug class should be suspended. Less common cardiac effects (hear block, arrhythmias, coronary syndrome) were reported mostly from the rheumatology cohorts who are at higher risk of cardiac disorders.[48]

It is hard to establish the relationship between demyelinating diseases and anti-TNF drugs, as IBD itself may be associated with demyelination. Patients with a family history of demyelination disorders are at higher risk; thus, other agents should be prescribed for these patients. In ceases who develop neurological deterioration suggestive for demyelination during treatment, anti-TNF discontinuation and neurology consultation should be sought.[55]

F-2- We suggest evaluation of neurologic symptoms in patients receiving ustekinumab to identify cases of posterior reversible encephalopathy syndrome (PRES) and discontinue the drug in suspected cases (GRADE: Weak D. Agreement 90%).

Some cases of PRES have been reported in clinical trials and post-marketing experience with ustekinumab. Clinical presentation included headaches, seizures, confusion, visual disturbances, and imaging changes consistent with PRES that recovered with supportive care following the withdrawal of ustekinumab. Monitoring of patients treated with ustekinumab for signs and symptoms of PRES and prompt administration of appropriate treatment and discontinuation of ustekinumab should be considered.[56]

F-3- We recommend discontinuation of vedolizumab when suspecting PML and never re-challenge it (GRADE: Strong D. Agreement 100%).

Although PML is very unlikely with vedolizumab, based on data about natalizumab-associated PML and regarding the poor prognosis of this adverse effect, discontinuation of drug and never re-challenging it, is recommended.[57]

F-4- We recommend discontinuation or decreasing the dose of tofacitinib in cases of hepatotoxicity (transaminase elevation to more than 3×ULN) (GRADE: Strong D. Agreement 100%).

F-5- We recommend discontinuation of tofacitinib when suspecting gastrointestinal perforation and never re-challenge it (GRADE: Strong D. Agreement 100%).

Patients treated with JAK inhibitors are at higher risk for abnormalities in LFT and gastrointestinal perforation. Transaminase elevation has been observed with all JAK inhibitors, especially in patients who are concomitantly treated with methotrexate. These abnormalities usually resolve with dose reduction or drug discontinuation.[58]

Gastrointestinal perforation events were mostly reported in patients who are also treated with nonsteroidal anti-inflammatory drugs or steroids. JAK inhibitors should be avoided in patients with a history of diverticulitis as they are at an increased risk of perforation. If perforation occurs while a patient receives a JAK inhibitor, further use of JAK inhibitors should be avoided.[59]

G- Infections

IBD patients treated with immunosuppressive drugs, especially combination therapies, are at higher risk for opportunistic infections. Active disease is a risk factor for infection, as every 100 points increase in Crohn's Disease Activity Index was accompanied by a 30% increase in the risk of opportunistic infections. IBD therapeutic agents can be classified into four degrees of immunosuppression: 1. no immunosuppression (aminosalicylate and low dose topical steroids); 2. selective immunosuppression (vedolizumab); 3. low immunosuppression (lower dose of immunomodulators and higher doses of topical steroids); and 4. moderate-severe immunosuppression (anti-TNF drugs, ustekinumab, natalizumab, calcineurin inhibitors, tofacitinib, and ozanimod). The group of 'moderate-severe' immunosuppression is not completely clear, as data directly comparing different drugs are limited. Thus, clear differentiation between moderate and severe systemic immunosuppression is not possible. The degree of immunosuppression also depends on the mechanism of action, dose, duration, and route of administration. Corticosteroids, thiopurines, and anti-TNF drugs are associated with a higher risk of opportunistic infections, and combination therapy increases the risk by about three times; if two or three more drugs are added, the risk increases by 14.5 times. In general, corticosteroids increase the risk of fungal infections, thiopurines increase the risk of viral infections, and anti-TNF drugs increase the risk of viral, fungal, and mycobacterial infections.[60]

Screening for hepatitis A, B, C, HIV, Epstein-Barr virus (EBV), cytomegalovirus (CMV), varicella-zoster virus, and measles virus (if there is no documented past infection or vaccination for the latter two), ideally at diagnosis and especially before or during immunosuppressive treatment, is recommended for all IBD patients. Like general population, a Pap smear for human papillomavirus (HPV) screening is also considered.[60]

G-1- We recommend hepatitis A vaccination for sero-

negative high-risk patients, based on risk factors (GRADE: Strong D. Agreement 100%).

The manifestations of hepatitis A virus (HAV) do not seem to be different in IBD patients compared with general population. Laboratory findings include an increase in hepatic transaminases (above 1000 units/dL) and bilirubin levels (usually less than 10 mg/dL). According to the ECCO guideline, vaccination is required only for high-risk individuals or who live in or travel to endemic areas.[60] Treatment with immunosuppressants (especially anti-TNF drugs and treatment with more than two immunosuppressors) reduces the chance of seroconversion, so vaccination is recommended at the time of diagnosis or before starting moderate to severe immunosuppressors.[61]

The vaccine available in Iran is VAQTA, which is an inactivated vaccine. As Iran is an endemic area (many areas in the south and north of Iran are endemic areas), vaccination is recommended only in high-risk individuals and patients with negative serology.[62]

G-2- We recommend vaccination against hepatitis B in seronegative patients and testing anti-HBs antibody level 1-2 months after complete vaccination. If the level does not reach the desired level (>10 IU/mL), re-vaccination should be considered (GRADE: Strong D. Agreement 90%).

The prevalence of HBV in IBD patients is similar to general population and can manifest as acute and chronic infections. IBD patients should be tested for HBV infection (HBsAg, anti-HBs, anti-HBc) and vaccination status. Vaccination of seronegative patients is recommended. Patients on immunosuppression may have a significantly reduced response to the standard immunization. Serology testing (one to two months after the administration of the last dose of HBV vaccine) is suggested for assessing the need for revaccination. Yearly or every two years testing for anti-HBs seems to be a good practice, and if the patients lose seroprotection (anti-HBs level less than 10 IU/mL), a single booster dose should be administrated.[6]

G-3- We recommend treatment with tenofovir for HBsAg$^+$ patients for at least one week to 1 month before starting immunosuppressive drugs. Tenofovir should be continued for one year after stopping immunosuppressives. For HBsAg$^-$ and Anti-HBc$^+$ patients with prior anti-HBV therapy, HBV prophylaxis is not necessary. In patients without prior antiviral therapy with moderate risk of reactivation, pre-emptive approach can be considered (GRADE: Strong D. Agreement 100%).

Reactivation of HBV is an established complication of immunosuppressants. It is recommended that chronic hepatitis B patients ideally start prophylaxis with tenofovir two weeks before the immunosuppressor therapy and continue antiviral prophylaxis for at least one year after the withdrawal of immunosuppressants. LFT and HBV DNA should be tested periodically (every 3 to 6 months) during treatment until at least 12 months after discontinuation.[60,64]

G-4- We suggest against starting biologics in patients with acute hepatitis C infection. In chronic cases of hepatitis C, direct acting agents can be started simultaneously with immunosuppression, but close monitoring of liver function should be considered (GRADE: Weak D. Agreement 90%).

The rate of hepatitis C infection in IBD patients is approximately the same as in general population. Acute infection is usually asymptomatic and becomes chronic in about 85% of cases. Since there is no active vaccine and prophylaxis program for HCV, general preventive measures should be considered. Testing should be performed by searching for anti-HCV antibodies; if antibodies are positive, HCV-RNA should be tested. If the infection is confirmed, patients should be managed according to the HCV clinical practice guidelines, ideally prior to starting biologics or immunomodulator therapy.[65] Immunosuppression may precipitate HCV-associated liver damage, and immunomodulators may result in cumulative liver toxicity, so management of infection with direct acting antiviral agents is critical in this population. If IBD treatment cannot be delayed, liver function should be monitored closely. There are no data regarding reactivation or exacerbation of the course of HCV in patient who were treated with biologics, and the safety profile of anti-TNF-α agents in HCV patients is favorable.[61]

G-5- We recommend HPV vaccination for young females and males. The HPV vaccines are not contraindicated in immunosuppressed patients (GRADE: Strong C. Agreement 100%).

Several studies have represented a higher risk of persistent HPV infection and cervical cancer in patients on immunosuppressive therapy. Thus, annual cervical screening and vaccination are recommended.[60] Because the HPV vaccine is inactivated vaccine, it can be administered to immunocompromised IBD patients. One study in young females with IBD reported immunogenic response without significant vaccine-associated adverse effects.[66,67]

G-6- We recommend annual influenza vaccination for all patients on immunosuppressive therapy, as they are at increased risk of severe influenza infection (GRADE: Strong C. Agreement 100%).

Annual influenza vaccination appears safe in IBD patients and is not associated with disease flares. Data suggest a lower efficacy of influenza vaccination in patients with IBD receiving immunosuppressants, especially those who receive combination therapy of an anti-TNF agent and azathioprine. However, there is no accepted strategy to improve efficacy. A recent meta-analysis reported that immunization against influenza is safe and immunogenic despite immunosuppression.[68]

G-7- We recommend induction therapy with anti-TNF drugs in patients with ASUC and CMV colitis, rapid tapering of corticosteroids, and delaying azathioprine until completing the antiviral course (GRADE: Strong D. Agreement 100%).

CMV infection reactivation detected by serology

is a common finding in IBD patients under immunosuppression. Low-level reactivation may disappear itself without complication. Small observational studies showed benefits for treating colonic CMV disease in UC patients, especially in steroid-refractory patients. There was enough evidence to support antiviral therapy in patients with moderate to severe colitis, especially in cases who are steroid-resistant with colonic CMV reactivation. The recommended treatment is intravenous ganciclovir (5 mg/kg BD) for 3–5 days, followed by valganciclovir (900 mg BD) for 2–3 weeks with infectious disease specialist advice. Systemic CMV reactivation (meningoencephalitis, pneumonitis, oesophagitis, or hepatitis) require prompt antiviral therapy and withholding all immunosuppressive therapies. Exposure to anti-TNF agents was not associated with an increased risk of CMV reactivation and was suggested as safe induction agents instead of corticosteroids in ASUC.[12,60]

G-8- We recommend against serologic testing for herpes simplex virus (HSV). In patients with frequent HSV recurrence, suppressive antiviral treatment should be considered (GRADE: Strong D. Agreement 100%).

Primary or recurrent oral and genital herpes seems to be more common, severe, and extensive in immunocompromised patients. There is no effective vaccine available for HSV. Patients should be asked about the history of HSV infection before starting immunosuppressive therapy. Routine prophylactic antiviral therapy with acyclovir (400 mg BD) or valacyclovir (500 mg daily) should be considered for patients with frequent recurrent attacks despite intermittent suppressive antiviral therapy. Immunosuppressive therapy should be withheld in cases of severe localized HSV infections including encephalitis, meningitis, pneumonia, esophagitis, and colitis.[60,61]

G-9- We recommend recombinant herpes zoster (RZV) vaccine for all IBD patients, especially those on immunosuppressive therapy, except for patients with documented vaccination or history of varicella. If RZV is not available, a live zoster vaccine (ZVL) can be used in immunocompetent patients with IBD and aged ≥ 50 years or low-dose immunosuppression (GRADE: Strong D. Agreement 90%).

Iran currently has no varicella vaccination program for varicella. Patients with a history of chickenpox or documented vaccination could be considered immune. Serological testing for VZV may be insensitive to detect low-level antibodies (may provide false-negative results) and should be used only in patients without documented infection or completion of the vaccination series. RZV is the preferred vaccine for patients with IBD disease, especially on immunosuppression. A ZVL is recommended in immunocompetent patients with IBD aged ≥ 50 years. ZVL vaccine is contraindicated in patients under moderate-to-severe immunosuppression and should be administrated four weeks before starting immunosuppressive therapy.[60] The Infectious Diseases Society of America (IDSA) stated that live varicella vaccines could be considered for non-immune patients on low-dose immunosuppression.[69]

G-10- We suggest against routine serologic tests for EBV unless for patients who want to start thiopurines. Use of thiopurines in EBV-IgG negative patients should be avoided (GRADE: Weak D. Agreement 90%).

EBV is associated with a higher risk of lymphoma in EBV-negative patients on immunosuppressive therapy (especially thiopurines), so the use of thiopurines in EBV-IgG negative patients should be carefully considered. Despite this concern, there is no established consensus to support the benefit of routine testing of EBV serology. Screening for previous EBV infection in patients prior to starting immunosuppressive therapy, especially thiopurines, seems reasonable. In cases who are EBV-IgG negative, thiopurine avoidance should be considered.[69]

G-11- We recommend treating IBD patients in time of COVID-19 pandemic should be similar to before the pandemic. In severe acute cases, stopping immunosuppressors may be considered (GRADE: Strong D. Agreement 90%).

G-12- In symptomatic PCR-positive COVID patients, starting biologics should be delayed for three days after improvement of symptoms (Good Practice recommendation, agreement 100%).

In general, current real-world experience is reassuring that IBD patients do not seem to be at increased risk of contracting SARS-CoV-2 or having a more severe disease course. According to data on over 1400 patients with IBD, compared with anti-TNF monotherapy, thiopurine monotherapy and the combination of thiopurines with anti-TNF agents were associated with a significantly increased risk of severe COVID-19, and 5-ASA may be associated with a higher risk of severe disease.[69] Anti-TNF agents[70] and JAK inhibitors[71] conferred a protective effect on COVID-19. The analysis of SECURE-IBD from inception (March 13, 2020) through May 21, 2021, suggests biologics and mesalamine are not associated with severe COVID-19 outcomes, and some medications may exert a protective effect. Furthermore, anti-TNFs combination with methotrexate might confer a lower risk of adverse COVID-19 outcomes than in combination with thiopurines. Corticosteroids appear to increase the risk of COVID-19 adverse outcomes, and tapering off the corticosteroids should be done when possible. These results also support the continuation of IBD medications that optimally treat their IBD during the COVID-19 pandemic.[72]

Because of the risk of IBD flare, we do not recommend withholding therapies or switching the drug for stable patients during the pandemic.

Whether to stop IBD treatment in patients who test positive for SARS-CoV-2 should be individualized according to risk-benefit evaluation.[60] Considering that medications confer a risk of ongoing immunosuppression, and pausing therapy may partially restore immune

function, we suggest deferring immunosuppressive therapy when possible until three days after the resolution of acute symptoms.

Patients with IBD should be vaccinated against SARS-CoV-2, and the best time to administer the vaccine is at the earliest opportunity. All available SARS-CoV-2 vaccines, including mRNA, vector-based, recombinant, and inactivated, are safe to administer to patients with IBD. Vaccination should not be delayed in patients who receive immunosuppressants; however, the vaccine efficacy may be decreased.[72] COVID-19 vaccination is associated with seroconversion in most IBD patients. The durability of responses is a concern, particularly in those receiving anti-TNF drugs and immunomodulators. In case of no response to initial series of vaccination, an additional dose may be helpful to acquire serological response in most patients.[73]

G-13- We recommend screening for latent tuberculosis (TB) infection before immunosuppression and consider re-screening patients who previously exposed to biologics and JAK inhibitors before switching drugs (GRADE: Strong C. Agreement 100%).

Exposure to biological therapies is associated with an increased overall risk of TB, both new diagnosis of primary TB and reactivation of latent TB. Screening for active or latent TB is crucial before starting anti-TNF drugs, other biologic therapy (ustekinumab and vedolizumab), or JAK inhibitors. Tuberculin skin test (TST) is likely to have false-negative results under immunosuppression. Therefore, interferon-gamma release assays (IGRA) should also be used.[75] Patient clinical data and chest radiography are also recommended for latent or active TB diagnosis.[60]

G-14- We recommend that active TB infection should be treated for at least 2 months before starting biologic or small molecule therapy (GRADE: Strong D. Agreement 100%).

G-15- We recommend that for patients with latent TB infection, chemoprophylaxis should be commenced at least four weeks prior to starting biologics and tofacitinib, except in cases of significant clinical urgency and with specialist advice (GRADE: Strong D. Agreement 100%).

The ideal timing for starting biologic or small-molecule therapy after commencing anti-TB treatment is not clear. In patients with active TB, biologics and JAK inhibitors should be deferred for at least two months of treatment with appropriate anti-tuberculosis regimen.[60,72]

In cases of latent TB infection, treatment with biologic drugs and JAKinhibitors should not be started for at least one month after commencing TB chemoprophylaxis. TST or IGRA may remain positive despite successful TB therapy; thus, close monitoring of clinical symptoms should be considered.[60]

G-16- Treatment of bacterial infections is usually similar to healthy population, but the duration of therapy should be longer. In septic patients, moderate to severe immunosuppression should be held until the improvement of acute symptoms (GRADE: Strong D. Agreement 100%).

Immunocompromised patients with IBD have an increased risk of pneumococcal infection, Legionella pneumophila, Salmonella, Listeria monocytogenes, C. difficile, and Nocardia.[60] Like other immunocompromised patients, IBD patients may present with atypical or nonspecific symptoms of infection. Bacterial infections should be treated according to the related guidelines and the result of culture susceptibility to antimicrobials. Antibiotic therapy tends to be more aggressive and with a longer duration because of the risk of severe and disseminated disease. Management of sepsis and severe infections should include dose reduction or cessation of immunosuppressants with consultation with an infectious disease specialist.[74]

G-17- We recommend Pneumococcal vaccination for all patients with IBD (GRADE: Strong D. Agreement 100%).

Bacterial pneumonia is one of the most frequent infections in immunocompromised IBD patients. A stepwise pneumococcal vaccination (PCV13 prime-PPSV23 boost) strategy, with an interval of at least eight weeks, is recommended by CDC for young children, adults > 65 years, and patients at risk for pneumococcal disease.[60] Both vaccines are available in Iran and should be administrated in immunocompromised patients with IBD.

G-18- We suggest standard Pneumocystis jirovecii pneumonia (PJP) prophylaxis with co-trimoxazole for IBD patients who are under treatment with three immunosuppressor agents (steroid, methotrexate, azathioprine, biologics). For patients under treatment with two immunosuppressors, especially when one agent is a calcineurin inhibitor, PJP prophylaxis may be considered (GRADE: Weak D. Agreement 90%).

The absolute risk of PJP (used to be called *Pneumocystis carinii*) is low; but is higher than general population. PJP chemoprophylaxis cannot be recommended in all IBD patients. However, chemoprophylaxis with TMP-SMX should be considered based on individual risk factors such as corticosteroid use (≥ 15 mg/d prednisone > 4 weeks), lymphopenia (< 200 cells/mm3), geriatrics (especially on steroids), and history of chronic pulmonary diseases. In patients on triple immunosuppressive therapy, PJP chemoprophylaxis should be considered. No PJP case associated with vedolizumab- or ustekinumab have been reported so far.[60] One case of PJP reported in association with tofacitinib. ESCEMID consensus recommended PJP chemoprophylaxis in tofacitinib-treated patients with risk factors, including high-dose corticosteroids.[75]

G-19- We recommend against the administration of live vaccines in patients receiving immunosuppressive therapy. It is recommended to wait for at least 1–4 months (based on the half-life of the immunosuppressor) after the termination of immunosuppressive therapy before administration of a live vaccine and wait for at least one month after live vaccine administration for starting immunosuppressors (GRADE: Strong D. Agreement 90%).

Ideally, immunization with live vaccines should be

done before the initiation of immunosuppression. A minimum interval of 3–4 weeks is adequate to cover the incubation period and clearance of vaccine virus before starting immunosuppressors. There is no established strategy for the optimal time of administration of the live vaccines in immunocompromised patients. However, considering drug elimination half-life, the suggested time interval between stopping immunosuppressants and live vaccination is one month for tofacitinib and 3-4 months for biological drugs.[60,76]

H- Malignancy

H-1- We suggest withholding anti-TNF drugs and thiopurines in IBD controlled patients who are diagnosed with cancer. In cases of active cancer and uncontrolled IBD, continuing or starting of immunomodulators and biologics can be considered (GRADE: Weak D. Agreement 80%).

H-2- We suggest that after the cure of cancer, restarting of anti-TNF drugs should be considered based on the recurrence rate of cancer. Treatment with drugs with low risk for cancer (ustekinumab and vedolizumab) is preferred (GRADE: Weak D. Agreement 80%).

There is an increased risk of intestinal and extra-intestinal cancers in IBD patients. Moreover, IBD therapies may impact cancer development and progression. Precise determination of the cancer risk associated with anti-TNF drugs is difficult because of the high rate of combination therapy, mostly with thiopurines.

In cases of current active cancer, withholding immunosuppression, especially thiopurines, should be considered. For patients who are on anti-TNF drugs, if IBD risk assessment indicates a high risk of IBD flare, anti-TNF drugs could be continued except in the setting of melanoma. In patients with IBD flare during active cancer on treatment, immunosuppressants and biologics should be avoided, while steroids and 5-aminosalicylates are safe. In cases of nonresponse to steroids, anti-TNF drugs could be prescribed with oncologist consultation. Vedolizumab and ustekinumab may be considered above anti TNF drugs.[77,78]

For patients with new IBDdiagnosis, determining the duration of complete recovery from prior cancer following its treatment is necessary. At least two years is required before starting immunosuppressants and anti-TNF drugs in cancers with low to intermediate risk of recurrence. For high-risk cancers with late chances of metastasis, a minimum interval of five years from cancer recovery is required. After two years, malignancy recurrence risk appears more favorable with methotrexate in comparison with thiopurines. Thiopurines should only be prescribed when there is no other option with the advice of an oncologist. Considering the risk of cancer, monotherapy with anti-TNF drugs appears relatively safe. Combination therapy with thiopurines should be avoided in the setting of prior cancer. If combination therapy is necessary, methotrexate should be preferred.[77,78] While newer gut-selective biologics appear safe, a firm conclusion cannot be made based on current data.

I- Extra- intestinal Manifestations

Manifestations of IBD are not restricted to the intestine, and many patients (12% to 35% in UC and 25% to 70% in CD) show concomitant associated EIMs such as musculoskeletal, metabolic bone disease, mucocutaneous, ocular, hepatobiliary, vascular, or hematologic. ECCO recommends considering anti-TNF drugs as possible options for IBD patients presenting with spondyloarthropathy, arthritis, mucocutaneous manifestations (such as pyoderma gangrenosum or erythema nodosum), scleritis or uveitis, as many EIMs share a pathogenic TNF-a dependent mechanism with IBD. Potential benefits of anti-TNF drugs in patients with the metabolic bone disease or coagulopathy is also described.[79]

I-1- We recommend that symptoms of IBD-associated arthropathies should be managed with control of intestinal inflammation, physiotherapy, and simple analgesics. If spondyloarthritis cannot be controlled with these measures, sulfasalazine, methotrexate, anti-TNF drugs, or tofacitinib may be considered (GRADE: Strong B. Agreement 100%).

Management of intestinal inflammation is an integral therapeutic target to control musculoskeletal manifestation. However, in a significant proportion of patients, the joint disease persists despite the amelioration of bowel inflammation. The preferred therapies for these patients are potentially effective drugs for both conditions. NSAIDs are effective for reducing pain and improving function. However, their use is controversial in IBD, as they can be associated with ulceration development in the small and large intestines and flares of IBD. COX-2 inhibitors have shown efficacy and safety in patients with quiescent disease for up to two weeks. Thus, short-term use might be acceptable for symptom relief in inactive intestinal disease with close monitoring of the bowel inflammation. Both infliximab and adalimumab have demonstrated efficacy in the management of IBD arthropathy, including axial disease.[79] Ustekinumab can be effective for IBD-related peripheral arthritis, but it is not effective in axial spondyloarthritis.[80]

I-2- We recommend the control of intestinal inflammation in IBD patients who develop nodosum erythema. Anti-TNF drugs may be considered in refractory or relapsing cases (GRADE: Strong C. Agreement 100%).

I-3- We recommend that in IBD patients with pyoderma gangrenosum who fail steroids treatment, anti-TNF drugs may be considered (GRADE: Strong D. Agreement 90%).

The most common mucocutaneous manifestations are erythema nodosum (EN) and pyoderma gangrenosum (PG). Controlling intestinal inflammation is the mainstay of the EN therapy. If treatment of intestinal inflammation is inadequate to control EN, corticosteroids or anti-TNF drugs have favorable efficacy.[80] PG treatment includes oral steroids, cyclosporine, tacrolimus, or anti-TNF drugs. Topical corticosteroids and topical tacrolimus are

effective in the treatment of early lesions.[81]

I-4- Most cases of anti-TNF drugs associated dermatological adverse effects can be managed with topical agents, and discontinuation of anti-TNF drugs is not required. Adding methotrexate or stopping anti-TNF drugs may be considered in refractory cases (Good Practice recommendation, agreement 100%).

Anti-TNF drugs may cause a wide spectrum of dermatological adverse effects, including injection site reactions, cutaneous infections, non-melanoma skin cancer, and psoriasis. Anti-TNF drugs are effective and approved for the treatment of moderate to severe psoriasis; however, they paradoxically induce psoriasis in some patients. In most cases, psoriatic lesions resolved after discontinuation of the causative anti-TNF drug. In some patients, skin lesions reappeared after the start of other anti-TNF drugs. Mild skin lesions are usually responsive to topical therapy, and trying continuation of anti-TNF therapy seems reasonable. In severe cases, treatment should include withdrawal of anti-TNF agent and administration of topical or systemic therapies for psoriasis.[82] Ustekinumab is an effective option for psoriasis that is not associated with drug-induced psoriasis.[83]

I-5- We recommend that uveitis may be controlled with anti-TNF drugs with ophthalmologists consult. Uveitis could also be a paradoxical effect in association with anti-TNF drugs and should be discontinued in these cases (GRADE: Strong D. Agreement 90%).

In IBD patients, anterior uveitis is described as an EIM. Contrary to episcleritis and scleritis, uveitis is less associated with intestinal inflammation. Uveitis can initially be treated with corticosteroid eye drops, and if not responsive, systemic steroids, immunosuppression, or anti-TNF agents can be prescribed with ophthalmologist consult. Ocular adverse events also may be considered a paradoxical effect of anti-TNF therapy. In these cases, anti-TNF drug withdrawal may be considered.[84]

I-6- We recommend against vedolizumab for IBD patients with EIM. If a patient on vedolizumab therapy develops EIM, adding an effective agent or changing the vedolizumab may be considered (GRADE: Strong, D agreement 100%).

There are limited data on the effect of vedolizumab on EIM. One study reported worsening EIMs in almost one-third of patients.[85] A temporarily increased risk for developing arthralgia has been reported under vedolizumab in 2-year follow-up[86] Until more data become available, we recommend against vedolizumab in patients with EIM.

J- Special Populations

J-1- We recommend that for elderly patients with IBD, vedolizumab and ustekinumab are considered preferred options, and tofacitinib should not be chosen in this population unless no other option is effective or tolerable (GRADE: Strong D. Agreement 90%).

Elderly onset IBD is defined when IBD is diagnosed at age > 60 years. IBD is increasingly diagnosed among elderly persons, and many IBDpatients live longer reaching older age. Although late-onset IBD is marked by colonic disease predominancy, milder disease course, and less frequent EIM, these patients are at higher risk of mortality because of comorbidities and polypharmacy. Pharmacotherapy for elderly patients is generally similar to younger IBD patients. The risk of infections, skin cancer, lymphoma, cardiovascular, and other side effects should be considered. As the safety profile of ustekinumab and vedolizumab seems good, these drugs are suggested as preferred options for elderly.[87]

Because of the increased risk of multiple comorbid conditions and pharmacokinetic changes, US FDA and the European Medicines Agency (EMA) have issued warnings regarding the infection and cardiovascular risks of tofacitinib in elderly patients.[79]

J-2- We suggest that in obese patients, infliximab with TDM is a good choice, as it administered on weight-based dosing. Adalimumab with standard dose and TDM should be considered, and increasing the dose of adalimumab may be needed (GRADE: Weak D. Agreement 90%).

J-3- We suggest in obese patients, ustekinumab, vedolizumab, and tofacitinib should be administered with standard dose. Close monitoring of response and adjusting the dose may be considered (GRADE: Weak D. Agreement 90%).

Following the increasing prevalence of obesity in general population, prevalence of obese-IBD patients may also be increased. It seems that there may be a link between the pathogenesis of IBD and obesity; however, it is not fully understood. Though pharmacokinetic data indicated that obesity might affect the absorption, volume of distribution, and clearance of the available drugs, the actual clinical consequences of these alterations on IBD management are less clear.[88]

It seems that weight-based dosing with infliximab is appropriate for IBD patients. However, there are some reports indicating treatment failure with adalimumab. A hypothesized explanation for the reported difference between adalimumab and infliximab-treated patients is the fixed-dosing schedule with adalimumab that resulted in inadequate doses for obese patients.[89] One study reported Body mass index is an independent risk factor for treatment failure in biologic-treated patients with UC, regardless of the dosing regimen.[90] We suggest that intravenous weight-based dosing with TDM is an appropriate strategy for obese patients.

The induction dose of ustekinumab is based on the patients' weight; however, there is no data to support weight-based dosing for vedolizumab and the maintenance dose of ustekinumab.[91] Based on results of OCTAVE study, the efficacy and safety of tofacitinib were similar in UC patients regardless of their baseline body mass index.[92]

J-4- We suggest that anti-TNF drugs can be continued during pregnancy. TDM before pregnancy is helpful for

adjusting the dose to decrease the risk of fetus exposure to inappropriate supra-therapeutic levels. Repeating TDM during pregnancy is not required, unless there are other reasons (GRADE: Weak D. Agreement 80%).

J-5- We suggest that in cases of anti-TNF drugs discontinuation during pregnancy, it can be restarted 24 hours after natural delivery or 48 hours after cesarean section (GRADE: Weak D. Agreement 90%).

Therapeutic decisions during pregnancy should be on an individual basis, especially for women who have failed several lines of therapy and for whom withdrawal of medications may confer higher risk.[93] Weight-based dosing using pre-pregnancy body weight should be considered for anti-TNF agents and the dose should be adjusted based on disease activity and serum concentrations. Serum levels should be tested before conception to avoid sub-therapeutic or supra-therapeutic concentrations. The increased risk of concerning birth defects following anti-TNF exposure during pregnancy has not been reported. Information related to this class of medications is emerging, but based on available data, anti-TNFs are considered safe during pregnancy.[94]

J-6- We suggest when discontinuation of vedolizumab or ustekinumab during pregnancy is not feasible: the last dose of the drug should be administrated 6-10 weeks before the expected date of delivery and drug be restarted 48 hours after delivery (GRADE: Weak D. Agreement 80%).

Vedolizumab and ustekinumab cross the placenta by active transport. Therefore, theoretically, they may influence fetal development. For vedolizumab and ustekinumab, the last dose should be given 6 to 10 weeks before the estimated date of delivery, and then restarted 48 hours postpartum.[94]

J-7- We recommend against treatment with small molecules in pregnancy and lactation, and these drugs (tofacitinib and ozanimod) should be discontinued before conception (GRADE: Strong D. Agreement 90%).

There are limited human data regarding tofacitinib exposure in pregnancy. Animal studies indicated a risk of malformation at supra-therapeutic doses, and based on this, it should be avoided during pregnancy. Tofacitinib half-life is approximately three hours, so a washout period of one week should be reasonable before conception.[94] While there has been limited clinical experience during pregnancy, based on data from animal studies, in utero exposure to ozanimod may cause fetal harm, and this drug should be avoided during pregnancy and for three months after stopping it.[95] Small molecules can be secreted in milk and should be avoided during lactation. The manufacturer and an expert panel recommend that breastfeeding while on tofacitinib should be stopped for 18 hours after the last dose.[94,96] Ozanimod and its active metabolites are highly bound in maternal plasma and unlikely to reach the breastmilk in large amounts; however, it is potentially toxic to the nursing infant. Because there is no published experience with ozanimod during breastfeeding, expert opinion recommends that a similar drug, fingolimod, should be avoided during breastfeeding, particularly for preterm infants.[97]

J-8- We recommend that anti-TNF drugs can be used during lactation; the decision to use vedolizumab and ustekinumab should balance the benefit of therapy to mother and potential risks to infant. (GRADE: Strong D. Agreement 90%).

In most studies, the concentration of anti-TNF drugs in milk is less than 1% of serum concentration, and these drugs are degraded in the stomach of the nursing child. Therefore, no harm from breastfeeding on biological therapies has been expected and described.[98]

Ustekinumab is usually not detectable in breast milk or found at very low levels. It is likely that ustekinumab is partially destroyed in gastrointestinal tract of infant, and also its absorption by infant is presumably minimal. If ustekinumab is required by the mother, it is not a reason to discontinue breastfeeding, and some experts consider it acceptable in lactation.[99]

Maternal vedolizumab injections appear to produce low levels in breast milk and do not adversely affect nursing infants. As vedolizumab is a large protein molecule, that may become destroyed in the infant gastrointestinal tract with minimal absorption. Most experts feel that the drug is probably acceptable during nursing.[98]

J-9- We suggest that vaccination with inactivated vaccines for newborns and infants from mothers on immunosuppressive drugs should be similar the other newborns and infants. Vaccination with live vaccines generally should be deferred by one year, and BCG vaccination should be delayed for six months. (GRADE: Weak D. Agreement 80%).

Avoidance of live vaccines in infants exposed to biological agents during the third trimester of pregnancy is recommended until at least six months after delivery. Given the possible deadly outcomes of disseminated BCG infection, live vaccines should be deferred by 6–12 months in breastfed infants of mothers exposed to anti-TNF agents. The rotavirus vaccine is the only live vaccine administered before six months in some countries, as case series reported safe administration. The first dose should be given before 15 weeks of age to be more effective in preventing rotavirus gastroenteritis

K- Switching and Discontinuation

K-1- We suggest that when there is a clinical need for rapid drug switching, it can be done immediately; however, when it is possible, 3-5 half-life should be considered as a wash-out period before starting the new drug (GRADE: Weak D. Agreement 80%).

Primary or secondary failure of a biologic may necessitate switching the treatment options. Before switching, optimizing the current biologic is necessary to avoid early exhaustion of therapeutic alternatives. The wash-out period is the drug-free interval between the discontinuation of current biologic and initiation of a second one. This period is generally calculated as three

to five times the biological half-life; however, there is no clear consensus.[100] Theoretically, a shorter interval could affect the pharmacokinetics and the safety profile of second drug. On the contrary, a longer wash-out period could have a harmful impact on the disease course. Two studies have reported that rapid switching did not impact the efficacy of second biologic; however, a higher rate of infections is possible. In the absence of direct recommendations, rapid switching or considering a wash-out period can be suggested depending on the need for a fast starting of therapeutic intervention and safety issues.[101]

K-2- We suggest careful decision for discontinuation of all medication in patients after two years of deep remission and without disease relapsing risk factors. Close monitoring of inflammatory markers and restarting therapy immediately after relapse diagnosis should be considered (GRADE: Weak D. Agreement 80%).

Several studies evaluated anti-TNF withdrawal in IBD patients and most of them reported relapse rates of 40–50% over two years following discontinuation of the anti-TNF. Fortunately, recapture of remission is relatively frequent in patients after restarting the therapy. To the best of our knowledge, no studies have evaluated clinical outcomes of the withdrawal of newer drugs. Decision-making regarding drug withdrawal must be individualized. Some studies have suggested predictive factors for relapse to guide decisions. Generally, these predictors can be categorized into poor prognostic factors, challenging disease course, and markers of active disease.[102] We suggest drug discontinuation for highly selected patients who are at clinical, endoscopic, radiological, and biochemical remission for two years with no poor prognostic factors. Close monitoring of disease activity should be considered to restart the drug immediately after any sign of disease recurrence.

L- Surgery

L-1- We recommend against holding anti-TNF drugs before IBD-related surgeries. If possible, surgery should be planned 4 weeks after the infliximab dose (2 weeks for adalimumab), and the next dose will be administrated 4 weeks (2 weeks for adalimumab) after surgery (GRADE: Strong D. Agreement 100%).

The relationship between using biologic drugs and perioperative complications of IBD remains unclear. The studies that represented a relationship between biologics and postoperative complications may have intrinsic indication bias as it can be more related to the severity of IBD that presented the indication for the biological therapy than biologic therapy itself. Data suggest surgery should not be deferred in severe cases as it may increase the risk of complications, including mortality.[103] If it is possible to delay the surgery, the surgery can be placed between two doses; for instance, if infliximab is prescribed every eight weeks, the surgery could be considered four weeks after the last dose and it can be restarted four weeks after the surgery.

L-2- We suggest against holding ustekinumab and vedolizumab before IBD-related surgery; however, vedolizumab can be associated with delay in postoperative wound healing (GRADE: Weak D. Agreement 90%).

Based on one multicenter observational study, patients who received ustekinumab preoperatively did not experience increased postoperative complications.[104] A limited case-matched analysis showed that preoperative biologic with ustekinumab and vedolizumab were not significantly different; and the choice between them should not be influenced by fear of surgical complications.[105] A possible increase in postoperative surgical site infections (SSIs) and overall infections associated with vedolizumab has been proposed. Although it is a gut-selective agent, blocking α4β7 integrin has previously been demonstrated to affect systemic M2 macrophages that are involved in systemic healing and tissue restitution. Impairing these cells by vedolizumab may predispose patients to superficial SSI poor wound healing, and mucocutaneous separation in stomas. However, the clinical effect of this proposed mechanism needs further validation.[106]

L-3- We suggest holding tofacitinib one week before surgery and restarting it 3-5 days after surgery, as it can be associated with infectious and thrombotic adverse effects after surgery (GRADE: Weak D. Agreement 80%).

Regarding the black box warning of an increased risk of venous thromboembolism (VTE) in medically treated UC patients with tofacitinib, an increased risk of postoperative VTE events should be considered. Two SSIs were reported in patients who had received tofacitinib, but more studies are needed to elucidate the risk of postoperative infections after surgery.[107,108] Based on current available data, we suggest withholding tofacitinib on day before surgery and restarting it 3-5 days after surgery after assessing the risk of thrombosis and SSI.

L-4- We recommend against preoperative TDM to decide about the time of surgery (GRADE: Strong C. Agreement 100%).

Three studies have reported a lack of relationship between preoperative trough levels and postoperative complications. Thus, it seems that biologics are not directly influencing postoperative outcomes. Therefore, we suggest against utilizing trough levels to determine optimal surgical timing or determining the risk of postoperative complications.[109]

L-5- We suggest that for non-IBD related elective surgery, biologic drugs should be started two weeks after surgery (GRADE: Weak D. Agreement 100%).

According to studies in patients with rheumatologic disease, biologic drugs should be started two weeks after surgery due to impaired wound healing. In patients who are not at risk for IBD flare, one approach for elective non-IBD surgery is that surgery is scheduled for a half-life after the first dose, and the next dose is given 14 days after surgery.[110]

M- Combination Therapy with Biologics

M-1- We suggest that for patients with partial response to one biologic drug, the addition of another biologic from another class or small molecule may be considered. For patients with a history of treatment failure with all approved agents, starting two biologics with different mechanisms may be beneficial (GRADE: Weak D. Agreement 100%).

M-2- We suggest adding an anti-TNF drug to another class of biologics in IBDpatients with uncontrolled axial spondyloarthritis beneficial (GRADE: Weak D. Agreement 100%).

M-3- We suggest adding ustekinumab to treatment in IBD patients with uncontrolled psoriasis (GRADE: Weak D. Agreement 100%).

M-4- We suggest adding vedolizumab to another biologic in with controlled EIM and uncontrolled intestinal inflammation to control the intestinal inflammation, as vedolizumab is not effective for treating extraintestinal manifestations (GRADE: Weak D. Agreement 100%).

After ruling out the possible cause of treatment failure (non-compliance, inappropriate dosing regimen or administration), dual biologic or adding small molecule therapy may be an option in highly selected, refractory IBD patients at specialized centers. Although there are few data regarding the efficacy and safety of dual-targeted therapy (DTT), it might represent a promising strategy for refractory patients.[111] Two scenarios that could require DTT include "refractory intestinal inflammation" that could not be controlled with alternative therapeutic agents; and "double indication" in patients with both IBD and EIM, where at least one of them is active despite appropriate pharmacotherapy. High cost of DTT and the risk of serious adverse effects should be considered. Vedolizumab cannot be used for controlling EIM and should not be added in cases of uncontrolled EIM. When EIM is controlled, Vedolizumab should be administrated with another effective agent to control intestinal inflammation. Ustekinumab is a good option for patients who have resistant psoriasis and controlled intestinal inflammation with other biologic agents.[112]

Conclusion

We summarized the current state of consensus on different aspects of safety and efficacy of biologic and small molecules in adult IBD patients. The Consensus Group voted on several statements that, alongside with clinical judgment, may guide clinicians to optimize the pharmacotherapy of patients.

Competing Interests

The authors declare no conflict of interest related to this work.

Supplementary Files

Supplementary file contains Table S1.

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