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Review Article

Treatment Options in Inflammatory Bowel Disease: A Narrative Review

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic disabling disease, which its incidence seems to have a significant increase during the last decade, especially in Iran. This is a narrative review regarding IBD treatment options including conventional and biological treatments, their indications, and their adverse effects. At the end, there is a brief discussion regarding IBD in special groups such as in pregnant women and the effect of nutrition in IBD.

Keywords: Inflammatory bowel disease, Treatment, Pregnancy, Nutrition

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disease consisting of ulcerative colitis (UC) and Crohn's disease (CD), which is estimated to affect 40.67 per 100000 subjects in Iran in 2012. Its incidence seems to have a significant increase during the last decade (1). The pathophysiology of this disease is basically because of dysregulation of normal immune response to luminal bacteria and inappropriate immune response to normal luminal flora (2). According to a mini review in Iran, the pattern of IBD is different in Iran, regarding sex distribution and extra-intestinal and intestinal manifestations, in comparison with other Asian countries (3). IBD causes significant intestinal and extra-intestinal manifestations, which besides increased mortality and morbidity, severely impairs the patients' quality of life.

Since past, there have been significant changes in the treatment of IBD. Treatment options are individualized based on severity, location, and complications. There are two major approaches in the treatment of IBD: conventional versus biological treatments. The "conventional" therapies include glucocorticoids and non-specific immunosuppressants, which are routinely used. In recent years therapeutic approaches have shifted towards biological, pathway based treatments including anti-tumor necrosis factor (TNF) drugs, anti-integrin antibodies and monoclonal antibodies as ustekinumab (4).The aim of this review is to explore the past and new therapies of IBD.

Conventional treatments

In spite of new treatment modalities the mainstay of treatment is still 5ASAs in mild to moderate IBD. Sulfasalazine and Mesalazine are from a group of anti-inflammatory drugs, which are recommended for induction and maintenance treatment of mild to moderate UC (5).These drugs are in different forms

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including tablet, suppositories, and rectal enema. It has been suggested to start with 3-4 gram, oral, per day in divided doses at ≤ 8-hour intervals, however, a recent Cochrane analysis showed that once daily 5- Aminosalicylic acid (ASA), has no difference with its multiple dosing in the treatment of UC (6) and even better (7). Combination of oral and rectal is better than each alone (8). In left side UC, using topical drugs such as suppositories or enema would be enough. According to a meta-analysis, the efficacy of using rectal ASA in managing UC is same to rectal corticosteroids (9). Moreover it has been suggested that dosage of 4.8 mg per day and 2.4 mg per day are effective in induction and remission of UC, respectively (10). Usually the dose of the drug that has been used for the induction of treatment will be continued in the maintenance phase. Recent European guidelines considering using 5-ASA in CD, suggest high dose of sulfasalazine (3-6 mg) only in mild colonic CD and not in small bowel involvement (11). These drugs are commonly used in pregnant patients. Based on a meta-analysis in Iran, the odds ratio of developing still birth (with maximum odds ratio), preterm delivery, congenital abnormalities, spontaneous abortion, and low birth weight (with minimum odds ratio) do not significantly increase in such mothers (2,12). ASA drugs may cause headache, nausea, vomiting, rash, diarrhea in less than 4-6%, and very rarely pancreatitis and renal toxicity (13). Women breastfeeding while on 5-ASA should be informed of the rare risk for diarrhea in newborn.

Budesonide is a corticosteroid with high topical anti-inflammatory activity and low systemic activity due to rapid first pass hepatic metabolism. Corticosteroids inhibit protein synthesis and transcription of inflammatory cytokines. A Cochrane review indicates that, budesonide is more effective than placebo and mesalamine, but less effective than conventional steroids in patients with CD, however, it is not effective in maintenance therapy. Budesonide multi matrix system technology (MMX) is a new treatment option for induction of remission in mild to moderate UC, due to releasing budesonide at PH > 7.0 (6). CORE 1 and 2 studies showed that budesonide MMX, 9 mg daily were 3 times more effective than placebo in UC remission (14). However trials for budesonide MMX, 6 mg daily for maintenance of remission did not show significant results comparing with placebo, however further studies are needed. In a retrospective cohort study in patients with CD, budesonide in outpatient setting is associated with lower likelihood of admission rate (15). Ulcerative Colitis, although shows minor involvement of the disease, may cause severe morbidity. A recent double blind study showed that 4 mg budesonide suppositories were superior to 2 mg of the drug, and there was no significant difference between budesonide and 5-ASA suppositories (16).

In patients who are not responding to 5-ASA, or in cases of recurrent flairs, we have to use immunomodulators such as azathioprine (AZA) and methotrexate for maintenance therapy after induction phase with steroids or biological drugs.

azathioprine is a prodrug of 6-mercaptopurine, which blocks purine synthesis, and is indicated in maintenance of remission in IBD, in steroid dependent patients, and fistulous CD (17). The recommended starting dose by Europian Crohn's and Colitis Organization is 1.5-2.5 mg/kg/day (18). Practically, we usually start with low dose (50 mg/day) and increase the dose every 2 weeks to reach the optimum dose. It should be noted that the effect of this drug may take about 3-4 months to begin. It has shown that monotherapy with AZA is not effective for remission induction in CD, but moderately effective in maintenance of steroid-induced remission (13). Previous studies showed that older patients (especially those aged over 50 years) and young men aged below 30 years treated with AZA are at increased risk for lymphoproliferative disorders, specially EBV(Epstein Bar Virus) positive ones. Exposure more than 1 year is needed for developing lymphoma and this risk of developing lymphoma is cut, after discontinuation of the drug (19).

Considering the metabolism of AZA, it has two metabolites, 6-methyl-mercaptopurine (6MMP), which is hepatotoxic, and 6 thioguanine nucleotides (6TG), which has myelosuppressive effect. Allopurinol, by inhibiting xanthine oxidase, shunts AZA metabolism to 6-TG pathway, reduces hepatotoxicity, and improves its efficacy. In patients not responding to AZA, with elevated liver enzymes and 6MMP levels, for better response to AZA and reduction of liver toxicity, co-therapy of AZA and

allopurinol has been suggested, however, such a treatment should be with 25% of ideal initiating dose of AZA and 200 mg allopurinol (20). Careful monitoring of blood count should be done for possible myelosuppression. Moreover it has been suggested that in patients with CD, taking AZA in combination with 5-ASA can increase the risk of elevated 6-TTG concentration and leukopenia (13).

In general the side effects of AZA are seen in 10-15% of patients with IBD, which are divided in two groups of dose dependent and idiosyncratic. Hepatotoxicity is an uncommon adverse event of AZA in patients with IBD, which is classified as idiosyncratic reaction. Although 6-MMP is hepatotoxic, the correlation between this metabolite concentration in blood and hepatotoxicity is poor. As a result, in a responder patient with normal aminotransferase level and elevated levels of 6-MMP, there is no need for dose reduction of AZA, but closer follow-up is necessary in such patients. It has been suggested that splitting the dose of AZA (twice a day), may be effective in reducing MMP concentration in these patients and reducing hepatotoxicity. In general, the suggested interval for monitoring liver enzymes is, 1 month after AZA initiation and then every 3-6 months (17). Increased dose of AZA should be accompanied by weekly monitoring of liver enzymes for one month and then monthly for 2 months (13).

Moreover live vaccines are contraindicated in these patients. However Centers for disease control and prevention center has proposed that patients with IBD regardless of treatment options should receive non-live vaccines including *influenza*, *pneumococ*, and *human papilloma virus* (HPV) and *Hepatitis B virus* (HBV) vaccines. Patients should be advised to use sun-protection and educated regarding the increased risk of dermatological and gynecological malignancies and refer them for gynecological and skin examination to specialists for screening basal and squamous cell carcinoma yearly.

Methotrexate (MTX) is an established medication for steroid dependent patents with CD (25 mg stat, intramuscular rout, and then 15 mg/week) (21) and is used in combination with anti TNF drugs to prevent antibody formation. Side effects include gastrointestinal disturbances (which significantly improve with 5 mg folic acid daily), fatigue, leukopenia, liver fibrosis, hypersensitivity pneumonitis, and teratogenicity. Methotrexate monotherapy and combination therapy are effective in CD, both in induction and maintenance (21). Regarding the modes of drug administration, recent studies suggest that the bioavailability of oral MTX is very variable (22). Methotrexate, recently, is proposed as the first line immunosuppressive therapy because of its similar rate of effectiveness as AZA with lower risk of malignancies especially in hepato-splenic T cell lymphoma in young men and rapid onset of action. Moreover it should be noted that based on the case series, MTX therapy had 25% complete and 31% partial closure in treating fistulous CD (23). It should be noted that MTX is forbidden during pregnancy and breastfeeding, and usage of this drug should be stopped at least 3 months before conception (24). Methotrexate has no role in induction or maintenance of treatment in patients with UC (25). For old patients receiving anti-TNF we use methotrexate instead of AZA during combination therapy for prevention of antibody formation, due to lesser risk of myeloproliferative disease.

Mycophenolate mofetil (MMF) is another immunomodulator that inhibits DNA and RNA synthesis by reversible inhibition of related enzyme. Based on previous studies, it is a good choice when patients could not tolerate thiopurine. Moreover Smith and colleagues, suggest better effect in patients with UC/IBD (26). A recent randomized controlled trial showed promising results for MMF when starting 1000 mg daily dose for 15 days and then titrated to median dose of 1500 mg per day (27).

Tacrolimus is a calcineurin inhibitor that showed promising profile in patients with UC and CD. It is a rapid acting immunosuppressive drug with dose dependent nephrologic and neurological side effects. It has been showed that tacrolimus is more effective than anti-TNF in patients with moderate to severe UC, however it was not significant (8). Moreover it has been shown that local tacrolimus in form of suppository or enema in dose of 2-4 mg is useful in distal colitis. In fistulizing CD, 0.15-0.31 mg/kg oral tacrolimus or 0.5 mg/kg topical tacrolimus lead in fistula closure, however unfortunately we do not have tacrolimus enema in IRAN (28).

Infliximab, Adalimumab, Certolizumab pegol, Golilumab (anti-TNF α inhibitors)

Infliximab (IFX) is a 25% mouse, 75% human, Adalimumab (ADA) is a fully human, immunoglobulin G1 antibody, certolizumab pegol (CZP) a monoclonal Fab fragment with a high binding affinity to TNF alpha, and golilumab is fully human monoclonal immunoglobulin G1 antibody, that bind and neutralize TNF-α (28,29). They are of principle cytokines mediating the TH1 pathway in CD. However in Iran, only IFX and ADA are available. Anti-TNF drugs should be used in patients with UC who are resistant to conventional drugs and in high risk patients with CD.

Infliximab has a body weight based dosing, which is administered intravenously, however ADA and CZP have fixed dosing with subcutaneous administration; however the interval of treatment may decrease. Previous studies showed that initiation of treatment with anti-TNF antibody in all patients with CD is not recommended; however it is recommended in severe cases, patients with poor prognostic factors and complicated disease, such as extensive small bowel or upper GI disease, perianal, stricturing or penetrating disease, history of surgery due to IBD, onset of IBD in childhood, and need for corticosteroid at first presentation (26). Guidelines suggest these drugs in the treatment of active severe disease not responding to adequate course of steroid, immunosuppressive agents, or those who are intolerant or have contraindication for using such agents. Two approaches have been defined in treating patients with CD: top to down versus step up treatment. Recent data showed that although mucosal healing was higher in top to down treatment group in short term; however, there is no difference in these two approaches in long term with the risk of over-treatment in top to down group (23).

Based on a meta-analysis, ADA/IFX + AZA are the most effective therapies, compared with methotrexate, AZA/6-mercaptopurine, IFX, ADA, certolizumab, vedolizumab, or combined therapies with placebo, for induction and maintenance of remission in CD (30). In perianal CD, IFX ,ADA, and CZP all are good options for induction and maintenance treatment of perianal fistula. However, one study support ADA and specially IFX for perianal fistula even with higher doses (26).

Some studies suggest to measure IFX levels when there is a loss of response, high CRP level, and persistent mucosal lesions (31). In a review article assessing pharmacokinetics of anti-TNF drugs, male sex, high body mass index, and low serum albumin were associated with higher clearance level and less response (32). However it is important that, drug level should always be measured by the same assay in each patient. Moreover, albumin level has a direct association with IFX half-life (33).

There are two approaches of active and proactive monitoring of drug trough level. In active approach, we measure trough level and anti-drug antibodies at disease flares or loss of response to the drug. In general it has been suggested that in levels under 12 µg/mL in IFX group and, < 4.9 µg/mL in ADA group combined with undetectable anti-drug antibodies, benefit from escalating the drug dose, however if anti-drug antibody is present, it is better to switch the drug (34,35). In proactive method, drug concentration would be measured at prespecified time. Depending on drug level, the dose of drug will be escalated, before patients develop symptoms. Up to now, there is not enough data supporting proactive drug monitoring in all patients; however in fistulizing types, it would be a rational choice. Cohort studies showed that, scheduled maintenance therapy of IFX is significantly associated with lower antibody formation compared with episodic administration (36). Moreover some other environmental factors, including obesity and daily cigarette smoking is associated with loss of response to IFX (37,38). In a study evaluating second anti TNF treatment in treatment failure of patients with IBD, it was shown that the efficacy was related to the cause of failure with the first anti-TNF.

Failure to respond to anti-TNF drugs in patients with is divided to primary and secondary loss of response. Primary non-responds is defined as continuation of symptoms after 14 and 12 weeks of initiation of IFX and ADA, respectively. Risk factors for primary non-responders include small bowel involvement, smoking, longer duration of the disease, high fecal infliximab level in first days of treatment, and low CRP and albumin levels (8,13,22,24). In a Korean study, higher pre-treatment of hemoglobin level is associated with better response (27). Second group of patients includes those who respond to the

drug at initiation and lose response in maintenance.

Co-treatment of IFX with an immunomodulator to reduce disease activity, dose escalation and prevention of antibody formation has been shown in previous studies (39).However, co-treatment with ADA is less clear and controversial. Recent meta-analysis and systematic review showed that combination therapy of adalimumab has no benefit over monotherapy in induction and maintenance of treatment in patients with CD (40). However Baert and colleagues showed that patients who receive monotherapy with ADA are at increased risk of antibody formation (37).

Recent study suggests that, previous exposure to anti TNFs specially with at least 6 months gap, is a major risk factor for developing adalimumab antibody (38). In primary failure, the remission rate after switching from IFX to ADA is 30%.In secondary failure, which is reported to be 20-50% after 12 months of therapy, remission rate with second anti-TNF drug is 45%. Studies showed that remission rate after switching to second anti-TNF was the highest, 61%, when it is due to anti-TNF intolerance (41).

Regarding perianal fistula in CD, a retrospective cohort study showed significant difference in controlling fistula disease in IFX group (42) specially in higher doses of IFX (10 mg/kg vs. 5 mg/kg) .

Adverse effects of anti-TNF therapy included dermatological consequences. The most prevalent dermatological side effects are psoriasis like lesions and cutaneous infections. Risk factors for developing cutaneous adverse events are younger age, CD, positive family history of cutaneous disease, and female sex. Neurological consequences of anti-TNF drugs include multiple sclerosis, Guillain-Barre disease, and aseptic meningitis. Anti-TNF could produce cardiac complications, such as congestive heart failure, and hepatic consequences such as reactivation of hepatitis B and autoimmune hepatitis (43). Other adverse effects include hematological disorders and malignancies (34).

Patients taking TNF inhibitors are highly immunosuppressed and should take influenza vaccine annually, and pneumococcal vaccine (13-valent, followed by 23-valent after 8 weeks and then every 5 years). It is recommended that all patients with aged 11-26 years should get human papilloma virus vaccine.

Recent data showed that infliximab is safe in pregnancy, even in third trimester, however caution is steel needed in using live vaccines for infants of mothers taking anti-TNF for at least 6 months after birth (40,44). However in patients in remission, it has been suggested that the last dose of anti-TNF should be at 22-24 weeks of gestation because the transfer of anti-TNF drug from placenta is most efficient in the second and third trimester, for the sake of least exposure to the fetus (45).

Anti-integrin antibodies (natalizumab, vedolizumab, etrolizumab)

IBD occurs due to infiltration of leukocytes in intestinal mucosa. This infiltration is dependent on surface expressed α4β7 integrins and mucosal address in cell adhesion molecules on endothelial cells (5). These drugs include vedolizumab, which targets an epitope comprising the α4β7 heterodimer, natalizumab, which recognizes the a4 integrin subunit, and etrolizumab, which is specific for the β7 subunit.

Recommended dose for patients with UC and CD is 300 mg intravenously over 30 minutes at 0-2-6 weeks and then every 8 weeks. If there was not any therapeutic benefit in week 14, the drug should be discontinued. Adverse reactions include hypersensitivity, headache, opportunistic infections, and progressive multifocal leukoencephalopathy (PML). However, PML infection, a fatal consequence of anti-integrins has been only seen with natalizumab, and not with vedolizumab, every patient with neurological symptoms should be evaluated for PML (46). Based on previous studies it seems that vedolizumab is a safe drug during pregnancy (47). A systematic review and meta-analysis in 2015 reported that vedolizumab and natalizumab showed significant increase in remission and clinical response, compared with placebo, especially in patients with UC. It seems that because of more specified target of anti-integrins, these drugs are superior to anti-TNF except in perianal fistulizing disease, extra-intestinal manifestations, and operative recurrence in IBD (48). Due to a cohort study in USA, active perianal disease, severe disease, prior anti-TNF usage, and smoking status were associated with increased risk of treatment failure with vedolizumab (49).

Biosimilars (CT-P13: Remsima & Inflectra for infliximab)

Biosimilars are copy of an original biopharmaceutical with the same biological activity, safety, and efficacy (50). The major advantage of biosimilars, is their lower price. CTP13 is the first monoclonal antibody, infliximab biosimilar, which approved in Europe. Up to now, there are limited data regarding the clinical outcomes of CTP13. Farkes and co-workers in a multicenter study in Hungarian and Czech concluded that CTP13 induction therapy resulted in 82.5% clinical and 47.6% steroid free clinical remission. 60.3% mucosal healing was achieved in week 14 (51). In a retrospective multicenter study in Korea, CTP13 had comparable efficacy and safety with infliximab. In anti-TNF naive patients, the clinical response and remission rate at 54 weeks of treatment in CD were 87.5% and 75%, and in UC were 100% and 50%, respectively. The maintenance of efficacy of CTP13, after switching from IFX, was 92.6% in CD, and 66.7% in patients with UC. There was no adverse effect in anti-TNF naïve patients with CD, whereas in 11.8% of patients with UC, skin rash, infusion reaction, leukopenia, and B viral hepatitis reactivation were developed. One patient, switching from INFX developed arthralgia and skin rash with CTP13 (52). In a case series study conducted by Kang and colleagues in Korea, CTP13 had interchangeability to INFX, however one patient experienced arthralgia, and another patient lost response to CTP13 during the study (53). In a clinical monitoring by Keil and others, in Czech Republic in 2016, the patients treated with CTP13 showed significant decrease in CRP and activity index, both in UC and CD (54). Moreover these patients showed significant weight gain. CTP13 showed four complications including pneumonia, allergic reaction, herpes labialis, and phlebothrombosis of lower extremity.

Monoclonal antibodies

Interleukin 12 and 23 are the major pro-inflammatory cytokines in pathogenesis of CD, which differentiate CD 4 positive cells to T helper 17 and 1 cells, respectively. Ustekinumab and MEDI2070 are human monoclonal antibodies that block the receptor p 40 subunit of IL12/23 of leukocytes. In a Spanish cohort, sub-cutaneous ustekinumab was effective in patients with CD resistant to steroids and anti-TNF agents; however, previous bowel resection predicts treatment failure with ustekinumab (55). In a recent study on MEDI2070, a selective IL-23 antibody, showed clinical effect in patients with CD, who failed on anti-TNF (21).

Tofacitinib (JAK/STAT pathway inhibitor)

Jenus kinas (JAK) binds to cytokine receptor and by phosphorylating it, binds to STAT. This complex initiates transcription of inflammatory genes. In a group receiving 15 mg twice a day, it had significantly higher clinical response, remission rate, and endoscopic response comparing with placebo, in moderate to severe UC (56).

SMAD7 anti-sense

Transforming growth factor β1 (TGFβ1) is an anti-inflammatory agent, which needs SMAD 2 and 3 for its activity. On the other hand, SMAD7 that is over-expressed in patients with UC and CD, inhibits SMAD2,3 (17). Mongerson, is an oral SMAD7 antisense oligonucleotide, which showed clinical remission and response rate were significantly higher than placebo, with limited effect on median CRP levels (57).

Antibiotics in IBD

Previous studies have shown that antibiotic therapy is useful in induction of treatment in patients with UC; however in recent guidelines it is only recommended when suspected to *clostridium difficile* infection (58). Moreover another condition that we use antibiotics in patients with UC, is primary sclerosing cholangitis (PSC). Previous studies suggest that oral vancomycin has great benefit in these patients (59). Moreover the author's recent pilot clinical trial study showed that vancomycin had significant benefit in lowering alkaline phosphatase, symptoms, erythrocyte sedimentation rate, and gamma glutamine transferase (47).

Surgery in IBD

In patients with UC, surgery is indicated in the presence of dysplasia or malignancy, poorly controlled disease, recurrent UC flares, toxic megacolon, and

non-responders to maximum medical treatment (60). However in CD, surgery is indicated in perforation, massive hemorrhage, dysplasia, gastrointestinal obstruction, and abscess formation not responded to medical therapy (61).

IBD and Pregnancy

A systematic review conducted in Iran showed that, using AZA is accompanied by significantly higher congenital abnormalities in comparison with control group (62). European Crohn's and Colitis Organization reported that most IBD medications, except MTX and thalidomide, are considered safe. Available data suggest low risk experiences during pregnancy. Timing of the last dose of anti-TNF is based on mother's condition, but it is best advised to be around weeks 24-26. Moreover metronidazole and ciprofloxacin are contraindicated in the first trimester of pregnancy and during lactation period (11). In a multicenter study conducted in Japan there was no association between increasing the rate of congenital abnormalities and low birth weight compared with normal group (63).

Nutrition, supplements and IBD

The association between diet and IBD is not totally clear. In a study by Aaron and colleagues, it was shown that red meat, and some vegetables including tomato may exacerbate the symptoms (8). In our previous study, resveratrol that is a natural compound interference in oxidation and inflammation process, may decrease clinical activity and inflammatory factors and have a role in improving the quality of life of these patients (48). Among other supplements, vitamin D supplementation has good effects, on the other hand, iron sulfate may exacerbate intestinal inflammation (64).Moreover regarding probiotics, in our previous study using Lactobacillus Casei strain in mild to moderate UC, showed no significant effect in treatment of UC (65), which is consistent with a recent meta-analysis (66).

CONFLICT OF INTEREST

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

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