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Review

Treatment of Crohn's Disease: Induction of Remission, Maintenance, and Management of Remission Period: A Comprehensive Review

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Abstract

The treatment of Crohn's Disease (CD) depends on factors such as disease location, phenotype, severity, complications, and associated risks. The primary goals are to achieve remission, maintain remission, and promote long-term mucosal healing. For mild-to-moderate CD, treatment options include 5-ASA compounds, corticosteroids, and antibiotics. Mesalamine and sulfasalazine are effective for patients with colonic or ileocolonic involvement but are not effective for isolated ileal disease. Corticosteroids are commonly used to manage acute attacks and serve as a bridge to other therapies. Although metronidazole and ciprofloxacin are not superior to placebo for active luminal disease, they may be beneficial for managing disease complications. Moderate-to-severe CD requires a more aggressive approach. Corticosteroids are prescribed for short-term use but carry significant risks. Immunomodulators, such as thiopurines and methotrexate, are typically used for long-term maintenance. Biological therapies, including anti-TNF agents, anti-integrins, and IL-12/23-targeted therapies, have proven effective for both the induction and maintenance of remission. Emerging therapies, such as upadacitinib and risankizumab, show promise for patients with prior biologic exposure and those who have failed conventional treatments. In severe cases, treatment may involve parenteral corticosteroids or anti-TNF agents. Ultimately, treatment decisions should be tailored to the patient based on disease characteristics and individual response to therapy.
Keywords: Crohn's disease, biological therapies, treatment

GENERAL PRINCIPLES

In the treatment of Crohn's Disease, several factors are crucial to determining the appropriate approach. These include the disease location (ileocolonic, colonic, ileal, or upper gastrointestinal), disease phenotype (inflammatory, penetrating, or obstructive), severity (mild, moderate, or severe), the presence of complications (such as stricture, fistula, or abscess), and the patient's risk profile.[1] After induction therapy, the remission phase is guided by an assessment of remission. The initial response to treatment is typically observed within the first 2 to 4 weeks, while the optimal response is evaluated over a period of 12 to 16 weeks on average. The primary goals of treatment are to achieve clinical, endoscopic, and histological remission, maintain remission, and promote long-term mucosal healing.

MILD-TO-MODERATE ACTIVE, LOW-RISK DISEASE

5-ASA Compounds

Mesalamine (5-ASA) is an effective anti-inflammatory agent that works within the intestinal lumen. However, oral mesalamine has not been shown to be superior to placebo for inducing remission or achieving mucosal healing.[2] Sulfasalazine, a combination of sulfapyridine and 5-ASA, is effective at doses of 3 to 6 g/day for treating symptoms in patients with colonic or ileocolonic involvement but is ineffective for isolated ileal disease. Like mesalamine, sulfasalazine has not demonstrated superiority over placebo in achieving mucosal healing.[2] Rectal mesalamine preparations (suppositories or enemas) are frequently used based on disease location but offer limited benefit.[2]

Corticosteroids

Conventional systemic corticosteroids are primarily used to manage acute attacks. These medications are effective in both improving symptoms and inducing remission. Additionally, they serve as a bridge therapy, controlling symptoms until immunomodulatory or biological therapies take effect. Oral corticosteroids are preferred for mild-to-moderate active disease, while intravenous (IV) preparations are used for moderate-to-severe active disease.[2]

Budesonide MMX can be used short-term to induce remission in patients with ileocecal disease. It offers a high local effect with low systemic bioavailability.[2] For patients with ileal disease characterized by aphthous lesions, without increased wall thickness on cross-sectional imaging or doppler activity on intestinal ultrasound, and with low CRP and fecal calprotectin levels, locally effective mesalamine alone or combined with short-term budesonide may be used.

Antimicrobial Therapy

Metronidazole and ciprofloxacin have not shown superiority over placebo in inducing remission for active luminal disease. However, broad-spectrum antibiotics can help control pyogenic complications associated with Crohn's Disease.[3] Metronidazole may also be useful in preventing postoperative luminal disease recurrence, though it does not prevent disease relapse after discontinuation. Rifaximin may provide benefits in cases of mild-to-moderate active disease.[4] However, antimycobacterial therapy has not demonstrated any significant benefit.[5]

MODERATE-TO-SEVERE ACTIVE, MODERATE-TO-HIGH-RISK DISEASE

Corticosteroids

Oral and IV corticosteroids can be used to provide short-term symptomatic relief during disease flares in moderate-to-severe Crohn's Disease. However, systemic corticosteroids are not sustainable for long-term mucosal healing and should be used with caution. Even with short-term use, corticosteroids can cause serious side effects, including bone loss, hypertension, hyperglycemia, glaucoma, sleep disturbances, depression, hypoadrenalism, and weight gain.[6] The protective effect of corticosteroids on mucosa is inconsistent, even in patients who report symptomatic improvement. Corticosteroids are contraindicated in patients with the penetrating disease phenotype because they can increase the risk of disease progression. Systemic corticosteroids are not recommended for long-term maintenance therapy. While topical corticosteroids are widely used, their benefits remain limited.[2]

For active disease, the recommended prednisone-equivalent dose is 40 to 60 mg per day. After 1 to 2 weeks of treatment with this dose, the aim is to reduce the dosage by 5 mg per week initially, followed by 2.5 to 5 mg per week until corticosteroid therapy is completed within a maximum of 3 months. Approximately 20% of patients show no improvement in disease activity despite taking 0.75 mg/kg/day of prednisolone (or an equivalent corticosteroid) for 4 weeks. These patients are classified as steroid-refractory. Another common issue is steroid dependence, which affects about 33% of patients. Steroid dependence is characterized by the inability to reduce the prednisolone dose below 10 mg per day within 3 months of initiating therapy, or disease relapse within 3 months of stopping the medication.[2]

IMMUNOMODULATORS (IMMS)

Thiopurines (azathioprine 1.5–2.5 mg/kg/day and 6-mercaptopurine 0.75–1.5 mg/kg/day) should be used for the maintenance of remission, not for the induction of remission, since their onset of action is slow (ranging from 8–12 weeks to 6–9 months). Thiopurine methyltransferase (TPMT) activity can be checked to identify patients at risk of adverse events at the beginning of treatment.[7] Adverse effects may include bone marrow suppression, pancreatitis, diarrhea, abdominal pain, vomiting, hypersensitivity reactions, hepatotoxicity, infections, and malignancies (non-melanoma skin cancers and lymphoma).[8,9] Methotrexate (15–25 mg/week, subcutaneous) can be used for maintenance and in steroid-dependent patients. It is teratogenic. Adverse effects may include nausea, vomiting, hepatotoxicity, pulmonary toxicity, bone marrow suppression, and malignancy.[8,9] Thiopurines and methotrexate can be used as an adjunct to reduce immunogenicity to biological therapy.[10] They have a slow onset of action (8–12 weeks). Complete blood count and liver enzymes should be monitored routinely (every 3 months) during their use.

BIOLOGICAL THERAPIES

Anti-TNF agents (infliximab, adalimumab, certolizumab pegol)

These agents may be used alone or in combination in cases of inadequate response to corticosteroids, thiopurines, and methotrexate, as well as in cases of steroid refractoriness or steroid dependence. Their onset of action is rapid, occurring within 2 weeks. They are effective for remission induction, maintenance, steroid-free remission, and complete or partial mucosal healing.[2]

MAIN POINTS

- Disease severity and risk factors play a crucial role in determining the appropriate treatment for Crohn's Disease.
- Early intervention with biological therapies is recommended for patients at high risk.
- Corticosteroids provide effective short-term relief but carry significant risks and should be used cautiously.
- Immunomodulators and biological therapies are essential for both inducing and maintaining remission.
- Emerging therapies, such as upadacitinib and risankizumab, show potential for patients who have experienced treatment failure.

The combination of infliximab with IMM therapies is more effective than administering both agents separately due to a synergistic effect. Infliximab monotherapy should not be preferred unless IMM agents are contraindicated; IMM should be included in combination therapy even at low doses.[2] Data on combination therapy with IMM for adalimumab and certolizumab pegol are currently insufficient.[2] IMM drugs help reduce the development of antibodies to anti-TNFs during treatment. However, if anti-TNF therapy is initiated following IMM therapy failure, evidence supporting the continuation of IMM therapy is lacking. The decision regarding continued IMM therapy should be based on the specific indication and the anti-TNF agent chosen. If infliximab is selected, it should be combined with IMM. For adalimumab, monotherapy may be appropriate based on individual patient characteristics. If adalimumab is used after infliximab failure, IMM should be combined with it, although this is not typically recommended.[2] The level of evidence supporting the use of infliximab and adalimumab for the induction and maintenance of remission is stronger than that for certolizumab pegol.[2] In newly industrialized countries, the response to anti-TNF therapy may be suboptimal, possibly due to differences in local application protocols or regional prescribing and reimbursement conditions.[11] While infliximab may appear more effective than adalimumab for certain first-line biological indications (e.g., penetrating disease), no significant overall difference in efficacy or sustainability between infliximab and adalimumab has been demonstrated.[12-14] Table 1 shows the structure, route of administration, dosages, and available preparations of anti-TNF agents.

ANTI-INTEGRINS (VEDOLIZUMAB)

Vedolizumab, a selective α4β7 integrin inhibitor, specifically blocks leukocyte migration to the intestinal area. It can be used in cases of intolerance, inadequate response, or loss of response to anti-TNF or IMM therapy, as well as in cases of corticosteroid intolerance, dependence, or inadequate response. It is also suitable for patients with treatment failure involving these agents and may be considered before other agents, even without the condition of prior treatment failure.[2] Vedolizumab has a slower onset of action compared to anti-TNF agents, particularly in anti-TNF-experienced patients, where it takes approximately 10 weeks to take effect, compared to 6 weeks in anti-TNF-naïve patients. Combination with IMM therapy helps reduce the development of anti-vedolizumab antibodies. Studies have shown that combination therapy with vedolizumab and IMM reduces treatment failure rates in Crohn's Dis-

Table 1. Anti-TNF agents

	Infliximab*	Adalimumab	Certolizumab pegol
Structure	Chimeric mouse-human IgG1	Human IgG1	Pegylated Fab fragment against TNF-alpha
Route of administration	IV infusion	Subcutaneous (SC)	Subcutaneous (SC)
Starting dose	5 mg/kg (0, 2, 6. weeks)	160 mg (day 0) 80 mg (day 15)	400 mg (0, 2, 4. weeks)
Maintenance dose	5 mg/kg (every 8 weeks)	40 mg (every 2 weeks, starting from day 29)	400 mg (every 4 weeks)
Available preparations	Remicade ® (100 mg powder vial), Remsima ® (100 mg powder vial) Ixifi ® (100 mg powder vial)	Humira ® (20 mg-40 mg injector and 40 mg pen) Amgevita ® (20 mg-40 mg injector and 40 mg pen)	Cimzia ® (200 mg/mL injector)

*In patients with loss of response, the infliximab dose can be increased to 10 mg/kg every 8 weeks. If there is no response by week 14, discontinuation of treatment should be considered.
(Legend: TNF: tumour necrosis factor, IV: intravenous, SC: subcutaneous, PEG: polyethylene glycol, Fab: humanized antibody fragment antigen-binding region)

Table 2. Biological therapies other than Anti-TNFs

	Vedolizumab*	Ustekinumab**
Mechanism of Action	Selective α4β7 integrin inhibitor	IL-12/23 targeted therapy
Route of Administration	IV infusion	IV infusion, Subcutaneous (SC) injection
Starting Dose	300 mg (at weeks 0, 2, 6)	≤55 kg: 260 mg IV >55-85 kg: 390 mg IV >85 kg: 520 mg IV
Maintenance Dose	300 mg (every 8 weeks)	90 mg SC (every 8 weeks, starting from week 8)
Available Products	Entyvio ® (300 mg injection vial)	Stelara® (45 mg, 90 mg prefilled syringes and 130 mg concentrated solution vials)

* Vedolizumab reimbursement criteria by the Ministry of Health: For fistulizing, severe, or active luminal Crohn's disease in patients whose disease cannot be controlled despite at least one anti-TNF therapy.
** Ustekinumab reimbursement criteria by the Ministry of Health: In cases of fistulizing, severe, or active luminal Crohn's disease where disease activity cannot be controlled despite treatment with at least one anti-TNF agent for 3 months.
(Legend: TNF: tumour necrosis factor, IL: interleukin, IV: intravenous, SC: subcutaneous)

ease compared to vedolizumab monotherapy. However, this effect has not been observed in ulcerative colitis.[15] Meta-analyses indicate that the combination of adalimumab or infliximab with azathioprine is more effective than vedolizumab for both the induction and maintenance of remission.[7-16]

IL-12/23-TARGETED THERAPIES (USTEKINUMAB)

Ustekinumab may be preferred for anti-TNF-naïve patients or in cases of treatment failure with corticosteroids, thiopurines, methotrexate, and anti-TNF agents.[17] It has a favorable safety profile, with no documented increase in the risk of serious infections or malignancies.[17] Table 2 presents the structure, route of administration, dosages, and available preparations of biological therapies other than anti-TNF agents.

GENERAL APPROACH TO BIOLOGICAL THERAPIES

- Biologic treatment-naïve patients have stronger evidence supporting the use of infliximab, adalimumab, ustekinumab, and vedolizumab for remission induction compared to certolizumab pegol.[10]
- Ustekinumab or vedolizumab is recommended for remission induction in cases of primary non-response to anti-TNF agents.[10]
- In cases of secondary non-response to infliximab, a different class of medication (ustekinumab or vedolizumab) is primarily recommended for remission induction, although adalimumab may also be used at the physician's discretion.[10]
- If adalimumab was used as first-line therapy, infliximab may be preferred as a second-line therapy in cases of loss of response.[10]
- Early initiation of biological therapies (either as monotherapy or in combination with IMM) is recommended in high-risk disease, without waiting for conventional treatment failure.[10]
- No prospective, controlled study has compared ustekinumab and vedolizumab when used as second-line biological therapies in Crohn's Disease. However, while real-world data suggest that ustekinumab may be more effective, some studies have shown equal efficacy.[13,14,18-21]

NEW THERAPIES

Approximately one-third of biologic-naïve Crohn's Disease patients are primary non-responders to anti-TNF agents. Additionally, one-third of patients who initially respond to anti-TNF therapy develop a loss of response or intolerance during treatment (secondary non-response). For secondary non-responders, treatment options include increasing the current dose, combining with immunomodulators, switching to another anti-TNF agent, changing to a different class of biological agent (e.g., anti-integrin or anti-IL-12/23), or switching to new therapies such as JAK inhibitors or p19 inhibitors.[2]

Upadacitinib (Selective JAK-1 Inhibitor)

Upadacitinib, a selective JAK-1 inhibitor, received FDA approval for the treatment of Crohn's Disease in May 2023 and Ministry of Health approval in February 2024. Data from completed phase-3 trials demonstrate that, in biologic-experienced patients with conventional treatment failure, upadacitinib achieved higher rates of clinical and endoscopic remission by week 12 compared to placebo. Furthermore, during the maintenance phase, clinical remission rates were dose-dependent. Upadacitinib also showed significantly higher improvement rates in patients with perianal disease compared to placebo.[22]

Risankizumab (Anti-IL-23)

Risankizumab has been approved by the FDA for the treatment of Crohn's Disease but has not yet been approved for this indication in Türkiye. Ongoing phase-3 trials have shown that, in biologic-experienced patients with conventional treatment failure, clinical and endo-

scopic remission rates at week 12 were higher with risankizumab than with placebo.[23]

SEVERE LUMINAL/INFLAMMATORY DISEASE

Parenteral methylprednisolone (40–60 mg/day) can be used for the treatment of severe or fulminant Crohn's Disease.[24] Anti-TNF agents (infliximab, adalimumab, certolizumab pegol) are also effective for managing severe active luminal disease.[10]

CONCLUSION

In conclusion, the management of Crohn's Disease requires a tailored approach based on individual patient characteristics. While traditional treatments, such as 5-ASA compounds, corticosteroids, and immunomodulators, remain essential, the introduction of biological therapies has significantly improved outcomes for many patients. New therapies, including upadacitinib and risankizumab, provide additional options for patients who have not responded to conventional treatments. Early intervention is crucial for high-risk patients to prevent disease progression and improve long-term outcomes. As research advances, it is likely that even more effective treatments will become available in the future.

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