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Maneuvering Clinical Pathways for Crohn's Disease

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Abstract

Purpose of review: Crohn's disease management has changed significantly with increasing use of biologics. Here we review the recent literature on the clinical management of Crohn's disease and new approaches in selecting and optimizing therapy. Recent findings: Recent studies have addressed the efficacy of proactive anti-TNFα trough level monitoring, the minimum effective trough level, the efficacy of biosimilars, and the efficacy and immunogenicity of newer biologics including anti-integrin therapy and anti-IL12/23 therapy. Optimizing anti-TNFα therapy according to trough concentrations correlates with improved remission rates. The biosimilars are non-inferior to the reference drug and patients can be switched from the reference drug to a biosimilar, or vice-versa, without a measurable change in efficacy, safety or immunogenicity. Anti-drug antibodies against the reference drug will also cross-react and neutralize the biosimilar. Immunomodulators are effective in decreasing immunogenicity and boosting anti-TNFα drug level. The anti-integrin and anti-IL12/23 therapies are effective as induction and maintenance therapy with low immunogenicity and excellent safety profiles. Patients with high-risk for post-operative recurrence should be started on a biologic therapy within 4 weeks post-op.

Summary: Treatment of Crohn's disease should be individualized according to patient's risk profile. Multiple biologic therapies are currently available for treatment of Crohn's disease including anti-TNFα therapy, anti-integrin therapy and anti-IL12/23 therapy. The choice of first line therapy should be based on individual risk-benefit analysis, route of administration and patient preference. Patient with inadequate response should have their trough level checked and therapy optimized. Therapeutic prophylaxis for post-operative recurrence should be based on patient's risk factors.

Keywords

Crohn's disease; inflammatory bowel disease; anti-TNFα; anti-integrin; anti-IL12/23; infliximab; adalimumab; certolizumab pegol; natalizumab; vedolizumab; ustekinumab

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Introduction

The management of Crohn's disease has evolved significantly over the last decade (1–4). While the anti-TNFα agents accounted for virtually all biologic use prior to 2014, new biologic agents including vedolizumab and ustekinumab have been approved and are rapidly gaining market share. A new paradigm of optimizing biological drug dosing according to serum drug levels, and/or co-administration of immunosuppressants to boost drug levels and lower immunogenicity has emerged, with the goal of improving the clinical efficacy of the monoclonal antibodies. Evolving studies looking at the presence of biological markers in patients to predict the likelihood of success and the safety of the various classes of therapies has raised the possibility of personalized medicine, with possible beneficial economic consequences. In this review, we will discuss recent data on the optimal use of the biological therapies, updates in treatment and monitoring with the anti-TNFα agents, when and how to use the newer biologic agents, and how to integrate immunomodulators and steroids in the clinical pathways for management of Crohn's disease.

Disease Severity and Risk Factors

The optimal therapeutic regimen is individualized based on each patient's disease severity and risk factors (1). Individuals with mild disease are ambulatory, able to tolerate oral intake, has minimal to no weight loss, no complications such as intestinal obstruction or development of abscess and no systemic toxicity such as high fevers. Endoscopically, these individuals may have isolated erosions or very shallow ulcerations but do not have extensive or deep large ulcers. Individuals with moderate to severe disease have significant weight loss, anemia, intolerance to oral intake, fever and/or abdominal pain. Endoscopically these individuals may have diffuse or large deep ulcers affecting more than 1 segment of colon and/or small bowel. Individuals with fulminant disease are those with systemic toxicity such as high fever, intestinal obstruction, persistent nausea/vomiting, severe malnutrition, development of an abscess, and/or persistent symptoms despite corticosteroid or biologic therapy. Non-modifiable risk factors for severe and progressive disease over time include young age at diagnosis, penetrating/stenosing disease, ileal disease location, extensive bowel involvement and severe perianal disease. Modifiable risk factors include smoking and NSAIDs use (5, 6). In addition, biomarkers can be helpful for risk stratification. The rate of complicated Crohn's disease has been shown to increase as the number and magnitude of reactivity to microbial antigens increases (7, 8).

General Principles of Treatment

Current therapeutic approaches are focused on inducing remission then maintaining remission. There are several different targets of treatment including clinical remission, endoscopic/radiologic remission and histologic remission (9). While clinical trials in Crohn's disease often define clinical remission by a compilation score composed of disease-specific as well as generalized systemic issues, such as the Crohn's Disease Activity Index (CDAI) (10), in "real-life" a patient is often considered as in clinical remission when that person has no subjective symptoms of their disease. However, researchers and more recent clinical trials have shown that patients who meet the criteria for clinical remission

may continue to have endoscopic and/or histological inflammation in the bowel, despite having no symptoms (11, 12). An individual is in endoscopic and/or radiologic remission when there are no endoscopic lesions detected on ileocolonoscopy and/or the bowel appears normal on radiologic imaging. Evolution of clinical trial endpoints in the last decade has moved from simple clinical remission to a composite of clinical and endoscopic endpoints to meet the criteria of remission. (1). An individual is in histologic remission when segmental biopsies taken during ileocolonoscopy showed no evidence of active inflammation under the microscope. Studies and clinical trial data have shown that Crohn's disease patients who achieve endoscopic remission are less likely to be hospitalized, started on corticosteroids, or have surgery within one year (13). Deep remission is a new term in the nomenclature, and is considered achieved when an individual is in clinical, endoscopic, radiologic and histologic remission (14). At the current time, the requirement for histological remission has not been a primary endpoint in clinical trials. Modern treatment paradigms in Crohn's disease aim towards the induction and maintenance of both clinical and endoscopic remission. Clinical response should be evaluated within the first few weeks of therapy, although that timing may vary depending upon the treatment regimen and disease severity of the patient. Updated treatment recommendations suggest evaluating patients endoscopically or with an objective measure of inflammation such as fecal calprotectin or C-reactive protein within 6 months after initiating therapy and adjusting the medication doses and/or choices if endoscopic healing is not reached (1). For patients with Crohn's disease that is not accessible by endoscopic evaluation, radiographic monitoring for outcomes may be appropriate. Non-invasive measures such as measuring serum C-reactive protein, fecal calprotectin or fecal lactoferrin monitoring may be helpful if the patient has elevated levels with their bowel inflammation (15).

We will discuss treatment options below based on patient's disease severity and risk factors.

Mild disease with no risk factors

The modern biological agents to date have not been formally tested as induction therapies for mild to moderately active Crohn's disease. As a result, the data on therapies targeting this patient population is rather weak. Currently, only controlled ileal release budesonide 9 mg daily is FDA-approved for remission induction in this population. Systemic corticosteroids, mesalamine, sulfasalazine, various antibiotics, and probiotics have either been inadequately studied or have failed to convincingly show an induction benefit (1). Meta-analyses have shown a modest benefit of mesalamine at best. Mesalamine use should be limited to those patients with mild disease who respond objectively to therapy (4).

For maintenance of therapy, there is currently no FDA-approved therapy in this population. The best data exists for the thiopurines (azathioprine and 6-mercaptopurine; limited data on thioguanine) and methotrexate. Unfortunately, oral budesonide, mesalamine, sulfasalazine, antibiotics, and probiotics have failed to show convincing evidence of a maintenance benefit, and systemic corticosteroids are toxic and ineffective as well (16).

The biological agents are increasingly being used in this patient group, or in those who fail to maintain remission with the immunosuppressants, due to their efficacy and safety profiles.

Moderate to severe disease or patients with risk factors

For patients with moderate to severe disease at presentation or patients with risk factors for severe progressive disease, induction regimen should include systemic corticosteroids or biologic therapy (17, 18). If the corticosteroid route is chosen, oral prednisone should be given at 40 mg to 60 mg daily for 1 to 2 weeks. For patients who responded clinically to steroid induction, the steroids are tapered by 5 mg to 10 mg weekly. They are transitioned to an immunomodulator or biologic therapy for maintenance. The use of immunomodulators has changed in the biologic era. Due to their side effect profile, currently the best use of immunomodulators is to decrease immunogenicity of biologics or to boost biologic drug level. Updates regarding use of immunomodulators for patients with inflammatory bowel disease was published in a recent review (19). For patients not responding to oral prednisone induction, an alternative explanation for symptoms such as c. difficile infection or CMV infection should be ruled out. These patients should then be admitted for IV steroid rescue therapy or induction with biologic therapy or a calcineurin inhibitor.

The biologic therapies are now displacing the traditional corticosteroids as safer, and perhaps more effective agents to initiate in patients with moderate to severely active Crohn's disease, particularly those who have already had a course of corticosteroids, or with perianal disease. Currently approved biological therapies include anti-TNFα therapy, anti-integrin therapy and anti-IL12/23 therapy.

Agents that target TNFα

The anti-TNFα agents approved for treatment of Crohn's disease include infliximab, adalimumab and certolizumab pegol (20). They can be used as initial induction therapy or for patients that did not respond adequately to corticosteroid induction. The onset of effect is rapid, with patients frequently noting clinical improvement after 2 weeks of therapy. Before initiating anti-TNFα therapy, patients should be checked for latent/active TB and hepatitis B infection. Patients with latent or active TB should first initiate appropriate treatment prior to starting an anti-TNFα agent. An alternative biologic may be preferable in these cases. Patients who are hepatitis B surface antigen positive should receive treatment with anti-viral agents before initiating anti-TNFα therapy and have their hepatitis B status monitored throughout therapy. Again, an alternative biological agent may be a better option.

Patients induced into clinical remission with anti-TNFα agents should continue anti-TNFα agents as maintenance therapy. For patients in clinical remission, we recommend repeat endoscopy 6 months after initiating therapy to assess mucosal healing. For patients with inadequate clinical or endoscopic response, we recommend checking the trough level of anti-TNFα agents and adjust therapies based on trough level.

The field of therapeutic drug monitoring for the biological agents has been developing for a number of years, perhaps best utilized in patients on anti-TNFα agents. The therapeutic levels cited in clinical trials have been shown to correlate to improved patient outcomes (clinically and endoscopically), as well as fewer Crohn's-related hospitalizations and surgeries. Subsequent clinical investigations have utilized different laboratories and techniques. Many of the studies suggest a target "goal" trough level for the anti-TNF agents:

infliximab at 5 ug/mL, adalimumab at 7.5 ug/mL, and certolizumab pegol at 20 ug/mL (21). Other reports have suggested higher trough levels with infliximab ≥ 7 ug/mL and adalimumab ≥ 10.1 ug/mL (22, 23). We note that the above trough levels are recommended minimal therapeutic levels and we target higher trough levels in patients with inadequate response to therapy. Patients can have a low trough level either due to pharmacokinetics of drug metabolism/elimination or due to development of anti-drug antibodies. For patients with a low trough level and no anti-drug antibodies, we recommend either increasing the dose or decreasing the interval of anti-TNFα therapy. For patients with low trough level and low anti-drug antibodies, we recommend increasing the dose of anti-TNFα therapy, decreasing the interval of anti-TNFα therapy and/or add an immunomodulator in an attempt to decrease anti-drug antibodies and boost anti-TNFα drug level (19, 20). A retrospective review showed that in patients who developed anti-drug antibodies, clinical response was recaptured in 6/10 patients receiving thiopurine and 7/7 patients receiving methotrexate (24). A separate retrospective review showed that for patients who developed anti-adalimumab antibody, 11/23 patients (48%) were recaptured after an immunomodulator was added (25). Addition of an immunomodulator resulted in increased drug trough concentration levels and gradual elimination of anti-drug antibodies. For patients who previously responded to their anti-TNFα therapy but then lost response with a low trough level and high level of anti-drug antibodies, we recommend switching to a different anti-TNFα agent. Patients with high trough level and inadequate response may be either primary non-responders or have mechanistic escape if they have responded to anti-TNFα therapy in the past and subsequently lost response. We recommend switching to a biologic therapy with a different mechanism for patients that are primary non-responders or had mechanistic escape.

Several studies have been done comparing reactive monitoring of anti-TNFα therapy based on patient's therapeutic response vs. proactive monitoring based on trough concentration. An observational study of infliximab therapy showed that patients with proactive drug monitoring has a greater probability of remaining on infliximab therapy compared to controls, especially for patients who achieved infliximab trough concentration >5 ug/mL (26). The TAXIT trial targeted infliximab trough concentrations of 3-7 ug/mL and included patients with Crohn's disease and ulcerative colitis. For Crohn's disease patients with initial trough concentrations less than 3-7 ug/mL, optimizing the trough concentrations to 3-7ug/mL increased patients in clinical remission from 65.1 % to 88.4%, and decreased the mean CRP concentration. However, after the initial optimization phase, no additional benefit was seen in the trough-concentration based dose adjustment group compared with the clinically-based dose adjustment group (27). The CALM study evaluated whether a tight control algorithm using clinical symptoms and biomarkers improve outcomes in patients with moderate to severe Crohn's disease compared to clinical management. In the tight control group, fecal calprotectin >250 ug/g and serum C-reactive protein >5mg/L were used as additional treatment failure criteria for adalimumab dose escalation compared to clinical management group. In addition, the CDAI treatment failure criterion was different: CDAI ≥ 150 in the tight control group and CDAI ≥ 200 in the clinical group. A significantly higher proportion of patients in the tight control group achieved mucosal healing at week 48 (56 of 122 patients, 46%) than in the clinical management group (37 of 122 patients, 30%) (28).

Several biosimilars for infliximab and adalimumab have been approved. Because of the complex structure of biologics, and exact replica of the originator drug cannot be made. The biosimilars have the same amino acid sequences as the brand name drug but may have minor differences such as glycosylation patterns. Biosimilars are tested to have no meaningful clinical differences in efficacy and safety compared to the brand name drug. The NOR-SWITCH trial was a large multi-center randomized double-blind trial conducted in Norway with patients on infliximab therapy randomized to either continued infliximab therapy or switch to biosimilar CT-P13 (infliximab-dyyb). 482 patients were randomized in a 1:1 ratio and this included 155 patients with Crohn's disease. The study showed that the biosimilar CT-P13 was non-inferior to infliximab originator drug with a pre-specified non-inferiority margin of 15% (29). Although the single switch between originator and biosimilar infliximab compounds have been shown to be safe and effective, there are currently no published large trials of multiple switches between an originator monoclonal antibody and one or more biosimilars, nor between two biosimilars for the same compound (30). Importantly, if a patient develops anti-drug antibodies against the originator drug, they should not be switched to a biosimilar as the anti-drug antibody will also neutralize the biosimilar drug (31), and vice-versa.

Therapies that target intestinal adhesion molecules

The anti-integrin therapies inhibit leukocyte trafficking from blood vessel into the tissue. Natalizumab is an anti-α_4 integrin that inhibit leukocyte trafficking to multiple tissues. The α_4 integrin subunit can pair with either the β_1 subunit to form $\alpha_4\beta_1$ or with the β_7 subunit to form $\alpha_4\beta_7$ integrin. The $\alpha_4\beta_1$ integrin is responsible for leukocyte trafficking into the inflamed brain in patients with multiple sclerosis while the $\alpha_4\beta_7$ integrin is responsible leukocyte trafficking into the intestine in patients with Crohn's disease (32). Natalizumab can neutralize both $\alpha_4\beta_1$ and $\alpha_4\beta_7$ and is effective in the treatment of both multiple sclerosis and Crohn's disease (33). However, the development of progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab due to the lack of immunoregulation against the John Cunningham (JC) virus has relegated this agent as one that should only be used in patients who test negative for exposure to the JC virus, and is withdrawn from those who subsequently test positive (34). As a result, natalizumab is rarely ever used in Crohn's disease. Prescribers are required to review the updated medical policy regarding natalizumab and enroll in the "TOUCH Risk Evaluation and Mitigation Strategy (REMS)" program prior to prescribing this agent (34).

Vedolizumab is an anti-$\alpha_4\beta_7$ integrin antibody that inhibits leukocyte trafficking specific to the intestine. It does not inhibit leukocyte trafficking to the brain and does not pose an increased risk for PML or other known infections. Vedolizumab can be used as a first-line therapy in patients with moderate to severe Crohn's disease or used in patients who have failed other therapies (35, 36). Because of its relatively gut specific mechanism, it has the least systemic side effects amongst the currently available biologic therapies (36). The onset of clinical effect maybe slower with vedolizumab therapy compared with anti-TNFα therapy. While patient on anti-TNFα therapy may notice improvement after the first 2 loading doses, patients on vedolizumab therapy may not notice improvement until after the 1st maintenance dose. In a post-hoc analysis of the GEMINI2 and GEMINI3

trials, vedolizumab plus corticosteroids during the induction phase improved the induction of clinical response compared with either steroids alone or vedolizumab alone (37). In a prospective study involving 31 Crohn's disease and 16 ulcerative colitis patients, vedolizumab trough level < 19 ug/mL at week 6 were associated with need for additional doses given at week 10 and every 4 weeks thereafter (38). A French cohort study showed that median vedolizumab trough level at week 6 for patients with mucosal healing was 26.8 ug/ml and for patients without mucosal healing was 15.1 ug/mL (39). The long-term efficacy of vedolizumab is excellent. For patients with clinical response of vedolizumab at week 6 with available follow-up data, 83-89% of patients continue to be in clinical remission after 2 years (40). Those rates are adjusted to 69% at 2 years and 43% at 3 years when categorizing all patients without follow-up data as treatment failures. For patients who lost response to standard dosing of vedolizumab every 8 weeks, shortening the infusion interval to every 4 weeks recaptured approximately 20% of patients (40). Because of the low rates of immunogenicity (<1%) (41), we typically do not start vedolizumab in combination with a immunomodulator although this can be considered in patients who have previously developed antibodies to a different biologic therapy. Testing for vedolizumab levels can be considered in patients who have lost response, although given the very low immunogenicity levels, one might consider just decreasing the treatment intervals to 300mg q4 weeks.

Agents that target Interleukin 12 and/or 23

Ustekinumab is an anti-IL-12p40 antibody that is approved for treatment of moderate to severe Crohn's disease by the FDA in 2016. The p40 subunit either combines with the IL-12p35 subunit to form IL-12 or combines with the IL-23p19 subunit to form IL-23. Therefore, ustekinumab inhibits both IL-12 and IL-23. Ustekinumab is an effective induction and maintenance agent for patients that have previously failed anti-TNFα therapy or immunomodulators/glucocorticoids (42). Patients receive a single weight based IV loading dose of 260 mg (<55kg), 390 mg (55 kg to 85 kg) or 520 mg (>85kg), followed by subcutaneous injection of maintenance dose 90 mg every 8 weeks. Although optimal ustekinumab serum trough level has not been established, higher serum ustekinumab trough level was associated with higher clinical response rate in both UNITI-1 and UNITI-2 trials (42). In a cohort study, maintenance ustekinumab trough concentration >4.5 ug/mL was associated with higher endoscopic response, although the clinical response rate did not differ (43). Ustekinumab has a low immunogenicity, with only 2.3% of patients developed anti-drug antibodies at week 44 in the IM-UNITI trial (42). While ustekinumab was approved for treatment of Crohn's disease in 2016, it has been approved for treatment of psoriasis since 2008. Safety surveillance data of ustekinumab from a long-term registry of psoriasis patients demonstrated excellent long-term safety profile (44). There are currently no direct head-to-head clinical trials comparing ustekinumab vs. anti-TNFα vs. anti-integrin therapy as a first line therapy for Crohn's disease patients. The choice of first line therapy is at the discretion of patient and provider based on individual risk-benefit analysis, route of administration, patient preference and insurance coverage. A clinical trial is currently ongoing to answer this question (Clinicaltrials.gov: NCT03108326). A summary of current FDA approved biologic therapies is included in Table 1.

Fulminant disease

Patients with fulminant disease are typically hospitalized. Imaging studies such as CT or MR enterography are performed to evaluate disease activity and rule out complications (1). Abscesses should be drained. Obstructions should initially be conservatively managed with NPO, IV fluids and NG tube decompression. Patients are given IV methylprednisolone 40mg to 60 mg daily. For patients with no improvement after 72 hours of IV steroids, infliximab can be added for induction. Early repeat dosing of infliximab infusion or use of a non-protein based therapy such as a calcineurin inhibitor should be considered in patients fulminant Crohn's colitis with a low albumin level due to high infliximab drug clearance into the stool (45). Early surgical consultation is recommended. Patients not responding to medical management should be treated surgically.

Patients with perianal disease

Patients with perianal abscess and fistulas represent a particularly challenging group. It is strongly advised to consult an experienced Crohn's disease surgeon to co-manage these patients (46). Small perianal abscess <5mm can be treated with antibiotics (typically ciprofloxacin and/or metronidazole) and may not require surgical drainage. Asymptomatic simple fistulas typically do not require treatment. For symptomatic complex fistulas, a combination of medical and surgical therapy is required. An examination under anesthesia of the affected area is often needed to allow for adequate evaluation and treatment. Any abscesses should be drained and setons should be placed if needed to allow continued drainage.

The medical therapy with the best evidence for healing of perianal fistulas is anti-TNFα therapy - in particular, infliximab, which is the approved agent with dedicated studies for fistula treatment. Infliximab is often effective for treating complex fistulas in combination with setons (47, 48). Higher infliximab trough levels may be required for fistula healing, with one cross-sectional study showing that patients with fistula healing on average had an infliximab trough level of 15.8 ug/mL (49). Adalimumab also has data supporting its use for healing of perianal fistulas; one study suggested comparable efficacy to infliximab (50–52). The addition of antibiotics to infliximab or adalimumab is more effective than infliximab or adalimumab alone and should be considered initially until the abscess and/or fistula is completely drained or healed (53, 54). Some patients require chronic or recurrent antibiotics, most commonly ciprofloxacin or metronidazole. Certolizumab pegol may also be effective in treating Crohn's fistulas, although the results varied with some studies showing efficacy and others negative (55). Other therapies that have shown efficacy in fistula healing include thiopurines and tacrolimus, although the toxicity associated with tacrolimus therapy precludes long-term use (55). No dedicated clinical trial has evaluated the efficacy of vedolizumab and ustekinumab on perianal fistula healing. Subgroup analysis of the GEMINI2 trial for vedolizumab showed that 31% of vedolizumab maintenance group achieved fistula closure at week 52 compared with 11% in the patients who received placebo maintenance infusions. (56). In the IM-UNITI trial for ustekinumab, 80% of patients in the ustekinumab group showed a fistula response at week 44 compared with 46% of patients in the placebo group (55).

Post-operative management

Recurrence of Crohn's disease following a "curative" resection of diseased bowel with a primary anastomosis has been well-identified over many decades. The initiation or continuation of medical therapy with an intent to decrease the risk and severity of the recurrence is referred to as "prophylaxis". The decision to utilize prophylactic therapy, and the choice of such therapy, should be guided by the patient's risk for early Crohn's disease recurrence and patient preference. High risk patients include patients with penetrating disease, two or more previous surgeries, active smoking, duration of less than 10 years between diagnosis and surgery, young age at diagnosis, extensive bowel involvement and failure of prior immunomodulator or biologic therapy (2). All patients who are actively smoking should be advised strongly to quit smoking. In these high risk patients, biologic therapy should be started, ideally within 4 weeks after surgery, to help prevent or minimize post-operative recurrence. Anti-TNFα therapy is the most effective in preventing post-operative recurrence (57). Vedolizumab is commonly used although less effective than anti-TNFα agents in a retrospective study (58). Data on ustekinumab is just emerging. A recent retrospective study showed that for patients who failed anti-TNFα therapy prior to surgery, restarting anti-TNFα therapy after surgery has limited efficacy and a different biologic should be considered (59). However, one should clearly distinguish patients who already were destined to have surgery when the anti-TNFα agent was introduced (arguably the vast majority of cases) from those who truly showed disease progression despite adequate drug levels of the anti-TNFα agent.

The intermediate risk patients are non-smokers who have penetrating disease without a history of prior surgical resection and are naïve to immunomodulators or biologics. These patients can be treated with the biologics, or with immunomodulators +/− metronidazole, although the success rates are much lower with the immunomodulators. Patients at low risk for post-operative recurrence are those with long-standing disease, never had a prior surgical resection, not an active smoker and whose indication for surgery is short fibro-stenotic disease. These patients may not initially need routine post-operative medications, can be offered mesalamine, antibiotics, or the agents mentioned above. It is recommended that regardless of the decision and choice of starting post-operative prophylactic therapy, patients should undergo a subsequent ileocolonoscopy (ideally 3 to 6 months post-surgery) to document success of the treatment strategy selected. Patients without post-operative recurrence on surveillance colonoscopy (Rutgeerts' score i0 or i1; i.e. less than 5 small erosions in the neoileum or colon by the surgical site) should continue periodic colonoscopic monitoring (60). Those with recurrent disease (Rutgeerts' score i2 or higher) should be started on effective therapy or have their current therapy optimized (61).

Future

The expanded therapeutic options with new biologic agents approved in the last decade has brought an exciting era for the management of Crohn's disease. Currently there are no reliable predictors of which patient will initially respond to which biologic therapy and it is a trial-and-error approach. However, prior response to an agent in a particular drug class would argue to stay "within class" if subsequently switching therapeutic options. Future

development of predictive biomarkers may allow us to select biologic therapy based on each individual patient's profiles. Multiple novel agents are currently under development in various phases of clinical trials (62, 63). These novel agents with different therapeutic mechanisms will allow us to expand our therapeutic options for Crohn's disease patients in the future.

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Table 1.

Current FDA approved biologic therapies for the treatment of Crohn's disease

Class	Name	Brand Name	Reference / Biosimilar	Route of Administration	Dosing		Suggested Trough level
					Induction	Maintenance	
Anti-TNFa	Infliximab	Remicade	Reference	IV	5 mg/kg at week 0, 2, and 6	5 mg/kg every 8 weeks	≥ 5 ug/mL
	Infliximabdyyb	Inflectra	Biosimilar				
	Infliximabqbtx	Ixifi					
	Infliximababda	Renflexis					
	Adalimumab	Humira	Reference	Subq	160 mg at week 0, 80 mg at week 2	40 mg every 2 weeks	≥ 7.5 ug/mL
	Adalimumabatto	Amjevita	Biosimilar				
	Adalimumabadbm	Cyltezo					
	Adalimumabadaz	Hyrimoz					
	Certolizumab Pegol	Cimzia	Reference	Subq	400 mg at week 0, 2 and 4	400 mg every 4 weeks	≥ 20 ug/mL
Anti-α4 integrin	Natalizumab	Tysabri	Reference	IV	300 mg every 4 weeks	300 mg every 4 weeks	Not determined
Anti-α4β7 integrin	Vedolizumab	Entyvio	Reference	IV	300 mg at week 0, 2, and 6	300 mg every 8 weeks	Not determined
Anti-IL12/23	Ustekinumab	Stelara	Reference	IV for induction, Subq for maintenance	< 55 mg = 260 mg; 55-85 mg = 390 mg; >85 mg = 520 mg	90 mg every 8 weeks	Not Determined