



Maneuvering Clinical Pathways for Crohn's Disease

Thomas X. Lu¹ · Russell D. Cohen¹

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Abstract

Purpose of Review Crohn's disease management has changed significantly with increasing use of biologics. 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-TNF α trough level monitoring, the efficacy of biosimilars, and the efficacy and immunogenicity of newer biologics including anti-integrin therapy and anti-IL12/23 therapy. Optimizing anti-TNF α therapy according to trough concentrations correlates with improved remission rates. Patients can be switched from the reference drug to a biosimilar, or vice versa, without a measurable change in efficacy, safety, or immunogenicity. Immunomodulators are effective in decreasing immunogenicity and boosting anti-TNF α 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 at high risk for post-operative recurrence should be started on a biologic therapy within 4 weeks post-op.

Summary Multiple biologic therapies are currently available for treatment of Crohn's disease including anti-TNF α 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 for recurrence.

Keywords Crohn's disease inflammatory bowel disease · Anti-TNF α · Anti-integrin · Anti-IL12/23 · Infliximab · Adalimumab · Certolizumab pegol · Natalizumab · Vedolizumab · Ustekinumab

Introduction

The management of Crohn's disease has evolved significantly over the last decade [1•, 2–4]. While the anti-TNF α 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 have 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-TNF α 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, and 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.

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✉ Russell D. Cohen
rcohen@medicine.bsd.uchicago.edu

¹ Section of Gastroenterology, Hepatology and Nutrition, Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, IL 60637, USA

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 one 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 NSAID 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 1 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 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 the use of immunomodulators for patients with inflammatory bowel disease were published in a recent review [19]. For patients not responding to oral prednisone induction, an alternative explanation for symptoms such as *Clostridium 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-TNF α therapy, anti-integrin therapy, and anti-IL12/23 therapy.

Agents That Target TNF α

The anti-TNF α 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-TNF α 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-TNF α 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-TNF α 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-TNF α agents should continue anti-TNF α 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-TNF α 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-TNF α 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 disease-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 α agents: infliximab at 5 $\mu\text{g/mL}$, adalimumab at 7.5 $\mu\text{g/mL}$, and certolizumab pegol at 20 $\mu\text{g/mL}$ [21]. Other reports have suggested higher trough levels with infliximab ≥ 7 $\mu\text{g/mL}$ and adalimumab ≥ 10.1 $\mu\text{g/mL}$ [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-TNF α therapy. For patients with low trough level and low anti-drug antibodies, we recommend increasing the dose of anti-TNF α therapy, decreasing the interval of anti-TNF α therapy, and/or adding an immunomodulator in an attempt to decrease anti-drug antibodies and boost anti-TNF α 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-TNF α therapy but then lost response with a low trough level and high level of anti-drug antibodies, we recommend switching to a different anti-TNF α 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-TNF α 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-TNF α 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 have a greater probability of remaining on infliximab therapy compared to controls, especially for patients who achieved infliximab trough concentration > 5 $\mu\text{g/mL}$ [26]. The TAXIT trial targeted infliximab trough concentrations of 3–7 $\mu\text{g/mL}$ and included patients with Crohn's disease and ulcerative colitis. For Crohn's disease patients with initial trough concentrations less than 3–7 $\mu\text{g/mL}$, optimizing the trough concentrations to 3–7 $\mu\text{g/mL}$ 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 both clinical symptoms and biomarkers improves outcomes in patients with moderate to severe Crohn’s disease compared to clinical management alone. In the tight control group, fecal calprotectin >250 $\mu\text{g/g}$ and serum C-reactive protein >5 mg/L were used as additional treatment failure criteria for adalimumab dose escalation compared to the 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 that in the clinical management group (37 of 122 patients, 30%) [28]. These findings suggest that objective markers of inflammation control (i.e., CRP and/or fecal calprotectin) should be used along with the physician’s subjective determination of patient response when medically managing patients with Crohn’s disease.

Several biosimilars for infliximab and adalimumab have been approved. Because of the complex structure of biologics, an 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 multicenter 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). Four hundred eighty-two 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 inhibits 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 for 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 among the currently available biologic therapies [36]. The onset of clinical effect maybe slower with vedolizumab therapy compared with anti-TNF α therapy. While patient on anti-TNF α therapy may notice improvement after the first two loading doses, patients on vedolizumab therapy may not notice improvement until after the first 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 levels <19 $\mu\text{g/mL}$ at week 6 were associated with the 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 $\mu\text{g/mL}$ and, for patients without mucosal healing, was 15.1 $\mu\text{g/mL}$ [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 an 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 300 mg every 4 weeks.

Agents That Target Interleukin 12 and/or 23

Ustekinumab is an anti-IL12/23 p40 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-TNF α therapy or immunomodulators/glucocorticoids [42••]. Patients receive a single weight-based IV loading dose of 260 mg (<55 kg), 390 mg (55 to 85 kg), or 520 mg (> 85 kg), 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 μ g/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-TNF α 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](https://clinicaltrials.gov/ct2/show/study/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 40 to 60 mg daily. For patients with no improvement after 72 h of IV steroids, infliximab can be added for induction. Early repeat

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-TNF α	Infliximab	Remicade	Reference	IV	5 mg/kg at week 0, 2, and 6	5 mg/kg q8 weeks; increase to 10 mg/kg if needed	$\geq 5 \mu$ g/mL
	Infliximab-dyyb	Inflectra	Biosimilar				
	Infliximab-qbtx	Ixifi					
	Infliximab-abda	Renflexis					
	Adalimumab	Humira	Reference	Subq	160 mg at week 0, 80 mg at week 2	40 mg q2 weeks; increase to 40 mg q1 week if needed	$\geq 7.5 \mu$ g/mL
	Adalimumab-atto	Amjevita	Biosimilar				
	Adalimumab-adbm	Cyltezo					
Adalimumab-adaz	Hyrimoz						
	Certolizumab Pegol	Cimzia	Reference	Subq	400 mg at week 0, 2 and 4	400 mg q4 weeks; increase to 400 mg q2 weeks if needed	$\geq 20 \mu$ g/mL
Anti- $\alpha 4$ integrin	Natalizumab	Tysabri	Reference	IV	300 mg every 4 weeks	300 mg q4 weeks only	Not determined
Anti- $\alpha 4\beta 7$ integrin	Vedolizumab	Entyvio	Reference	IV	300 mg at week 0, 2, and 6	300 mg q8 weeks; increase to 300 mg q4 weeks if needed	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 q8 weeks; increase to 90 mg q4 weeks if needed	Not determined

dosing of infliximab infusion or use of a non-protein-based therapy such as a calcineurin inhibitor should be considered in patients with 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 < 5 mm 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-TNF α 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 $\mu\text{g/mL}$ [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 disease 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-TNF α therapy is the most effective in preventing post-operative recurrence [57]. Vedolizumab is commonly used although less effective than anti-TNF α agents in a retrospective study [58]. Data on ustekinumab is just emerging. A recent retrospective study showed that, for patients who failed anti-TNF α therapy prior to surgery, restarting anti-TNF α 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-TNF α agent was introduced (arguably the vast majority of cases) from those who truly showed disease progression despite adequate drug levels of the anti-TNF α 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 \pm 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, are not active smokers, and have an indication for surgery which is short fibro-stenotic disease. These patients may not initially need routine post-operative medications and 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 neoleum 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].

Personalized Medicine

The expansion of effective clinical options in patients with Crohn's disease has opened up the possibility of true "personalized medicine"; i.e., the decision to start a particular medicine may be based upon a multitude of factors that are unique to that individual. Personalization can be as simple as patient preference for a *mode of medication dosing* (intravenous vs. subcutaneous; perhaps oral if some of the small molecules undergoing clinical trials reach the market), *frequency of dosing* (every 2 months vs. every 2 weeks vs. daily), or *cost to the patient*. Biological parameters to consider for personalizing medication choices may be issues such as *disease phenotype* (i.e., the comparatively strong data for Crohn's disease fistula healing with infliximab, and perhaps the other anti-TNF α agents, when compared to other mechanisms), *the presence of extraintestinal or concomitant immune disorders* (i.e., patients who have Crohn's disease along with psoriasis might choose an agent such as ustekinumab or perhaps an anti-TNF α agent; those with rheumatoid arthritis would likely be best served by an anti-TNF α agent), *a previous personal or family history of lymphoma or another neoplasm* (in which case vedolizumab or perhaps ustekinumab might be a safer option than an anti-TNF α agent), or *a history of recurrent infections* (again, favoring vedolizumab or perhaps ustekinumab) in those individuals. Women planning *pregnancies* may prefer certolizumab (which does not cross the placenta) or one of the other anti-TNF α options (two decades of pregnancy safety data); safety during nursing may also be a factor that enters the equation when selecting effective therapy.

These examples of *shared decision making*, whereby the provider and patient thoroughly discuss the patient's current and future medical plans, preferences towards dosing, and comfort level with medication safety are concepts that have emerged in the past few years. Direct-to-consumer marketing, the widely available plethora of "medical advice" on the Internet, and patient access to their medical charts through modifications in the electronic medical record have all led to an increased demand for information prior to making an informed decision.

Future

The expanded therapeutic options with new biologic agents approved in the last decade have 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 and allow for an expanded personalization of medical care, for Crohn's disease patients in the future.

Compliance With Ethical Standards

Conflict of Interest Russell Cohen reports personal fees from Abbvie, Celgene, Janssen, Pfizer, and Takeda, outside the submitted work. Thomas Lu declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
- 1.•• Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: management of Crohn's disease in adults. *Am J Gastroenterol*. 2018;113(4):481–517 **This clinical guideline describes current recommendations for management of Crohn's disease in adults in the USA.**
 2. Nguyen GC, Loftus EV Jr, Hirano I, Falck-Ytter Y, Singh S, Sultan S, et al. American Gastroenterological Association Institute Guideline on the management of Crohn's disease after surgical resection. *Gastroenterology*. 2017;152(1):271–5.
 3. Gionchetti P, Dignass A, Danese S, Magro Dias FJ, Rogler G, Lakatos PL, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 2: surgical management and special situations. *J Crohns Colitis* 2017;11(2): 135–149.
 4. Gomollon F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *J Crohns Colitis* 2017;11(1):3–25.
 5. Yarur AJ, Strobel SG, Deshpande AR, Abreu MT. Predictors of aggressive inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2011;7(10):652–9.
 6. Klein A, Eliakim R. Non steroidal anti-inflammatory drugs and inflammatory bowel disease. *Pharmaceuticals (Basel)*. 2010;3(4): 1084–92.
 7. Choung RS, Princen F, Stockfish TP, Torres J, Maue AC, Porter CK, et al. Serologic microbial associated markers can predict Crohn's disease behaviour years before disease diagnosis. *Aliment Pharmacol Ther*. 2016;43(12):1300–10.
 8. Dubinsky MC, Kugathasan S, Mei L, Picornell Y, Nebel J, Wrobel I, et al. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clin Gastroenterol Hepatol*. 2008;6(10):1105–11.

9. Panaccione R, Colombel JF, Louis E, Peyrin-Biroulet L, Sandborn WJ. Evolving definitions of remission in Crohn's disease. *Inflamm Bowel Dis*. 2013;19(8):1645–53.
10. Freeman HJ. Use of the Crohn's disease activity index in clinical trials of biological agents. *World J Gastroenterol*. 2008;14(26):4127–30.
11. D'Inca R, Caccaro R. Measuring disease activity in Crohn's disease: what is currently available to the clinician. *Clin Exp Gastroenterol*. 2014;7:151–61.
12. Rutgeerts P, Gasink C, Chan D, Lang Y, Pollack P, Colombel JF, et al. Efficacy of ustekinumab for inducing endoscopic healing in patients with Crohn's disease. *Gastroenterology*. 2018;155(4):1045–58 **This endoscopic substudy of Crohn's disease patients who participated in one of the three pivotal trials with ustekinumab showed benefit in endoscopic improvement in as early as 8 weeks in patients with moderate to severe Crohn's disease.**
13. Orlando A, Guglielmi FW, Cottone M, Orlando E, Romano C, Sinagra E. Clinical implications of mucosal healing in the management of patients with inflammatory bowel disease. *Dig Liver Dis*. 2013;45(12):986–91.
14. Colombel JF, Louis E, Peyrin-Biroulet L, Sandborn WJ, Panaccione R. Deep remission: a new concept? *Dig Dis*. 2012;30(Suppl 3):107–11.
15. Mosli MH, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. *Am J Gastroenterol*. 2015;110(6):802–19 quiz 20.
16. Sandborn WJ, Feagan BG, Lichtenstein GR. Medical management of mild to moderate Crohn's disease: evidence-based treatment algorithms for induction and maintenance of remission. *Aliment Pharmacol Ther*. 2007;26(7):987–1003.
17. Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology*. 2015;148(2):344–54 e5 quiz e14-5.
18. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2008;2:CD006792.
19. Johnson CM, Dassopoulos T. Update on the use of thiopurines and methotrexate in inflammatory bowel disease. *Curr Gastroenterol Rep*. 2018;20(11):53.
20. Adegbola SO, Sahnun K, Warusavitame J, Hart A, Tozer P. Anti-TNF therapy in Crohn's disease. *Int J Mol Sci*. 2018;19(8).
21. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S, American Gastroenterological Association Institute clinical guidelines C. American Gastroenterological Association Institute Guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology*. 2017;153(3):827–34.
22. Drobne D, Kurent T, Golob S, Svegl P, Rajar P, Terzic S, et al. Success and safety of high infliximab trough levels in inflammatory bowel disease. *Scand J Gastroenterol*. 2018;53(8):940–6.
23. Bodini G, Giannini EG, Savarino V, Del Nero L, Pellegatta G, De Maria C, et al. Adalimumab trough serum levels and anti-adalimumab antibodies in the long-term clinical outcome of patients with Crohn's disease. *Scand J Gastroenterol*. 2016;51(9):1081–6.
24. Strik AS, van den Brink GR, Ponsioen C, Mathot R, Lowenberg M, D'Haens GR. Suppression of anti-drug antibodies to infliximab or adalimumab with the addition of an immunomodulator in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;45(8):1128–34.
25. Ungar B, Kopylov U, Engel T, Yavzori M, Fudim E, Picard O, et al. Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab. *Aliment Pharmacol Ther*. 2017;45(2):276–82.
26. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, Moss AC, Sandborn WJ, Cheifetz AS. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. *Inflamm Bowel Dis*. 2014;20(11):1996–2003.
27. Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Comperolle G, Van Steen K, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology*. 2015;148(7):1320–9 e3 **This study showed that optimizing initial trough concentration of infliximab increased the number of patients in clinical remission.**
28. Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vanasek T, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet*. 2018;390(10114):2779–89.
29. Jorgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haaavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 2017;389(10086):2304–16 **This study showed that patients with inflammatory diseases who were stable on originator infliximab could be switched to the biosimilar CT-P13 with no loss of efficacy or increase in immunogenicity when compared to those who stayed on the originator drug.**
30. Raffals LE, Nguyen GC, Rubin DT. Switching between biologics and biosimilars in inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2018.
31. Reinisch W, Jahnsen J, Schreiber S, Danese S, Panes J, Balsa A, et al. Evaluation of the cross-reactivity of antidrug antibodies to CT-P13 and infliximab reference product (Remicade): an analysis using immunoassays tagged with both agents. *BioDrugs*. 2017;31(3):223–37.
32. Kawamoto E, Nakahashi S, Okamoto T, Imai H, Shimaoka M. Anti-integrin therapy for multiple sclerosis. *Autoimmune Dis*. 2012;2012:357101.
33. Nelson SM, Nguyen TM, McDonald JW, MacDonald JK. Natalizumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2018;(8):CD006097.
34. Warnke C, Menge T, Hartung HP, Racke MK, Cravens PD, Bennett JL, et al. Natalizumab and progressive multifocal leukoencephalopathy: what are the causal factors and can it be avoided? *Arch Neurol*. 2010;67(8):923–30.
35. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369(8):711–21 **This study showed vedolizumab as an effective induction and maintenance agent in patients who had no response or unacceptable side effects from glucocorticoids, immunosuppressants, or anti-TNF α agents.**
36. Scribano ML. Vedolizumab for inflammatory bowel disease: from randomized controlled trials to real-life evidence. *World J Gastroenterol*. 2018;24(23):2457–67.
37. Sands BE, Van Assche G, Tudor D, Akhundova-Unadkat G, Curtis RI, Tan T. Vedolizumab in combination with corticosteroids for induction therapy in Crohn's disease: a post hoc analysis of GEMINI 2 and 3. *Inflamm Bowel Dis*. 2019.
38. Williet N, Boschetti G, Fovet M, Di Bernado T, Claudez P, Del Tedesco E, et al. Association between low trough levels of vedolizumab during induction therapy for inflammatory bowel diseases and need for additional doses within 6 months. *Clin Gastroenterol Hepatol*. 2017;15(11):1750–7 e3.

39. Yacoub W, Williet N, Pouillon L, Di-Bernardo T, De Carvalho Bittencourt M, Nancey S, et al. Early vedolizumab trough levels predict mucosal healing in inflammatory bowel disease: a multicentre prospective observational study. *Aliment Pharmacol Ther.* 2018;47(7):906–12.
40. Vermeire S, Loftus EV Jr, Colombel JF, Feagan BG, Sandborn WJ, Sands BE, et al. Long-term efficacy of vedolizumab for Crohn's disease. *J Crohns Colitis.* 2017;11(4):412–24 **This study showed that most patients with clinical response to vedolizumab at 6 weeks continue to have clinical response at 2 years.**
41. Al-Bawardy B, Ramos GP, Willrich MAV, Jenkins SM, Park SH, Aniwan S, et al. Vedolizumab drug level correlation with clinical remission, biomarker normalization, and mucosal healing in inflammatory bowel disease. *Inflamm Bowel Dis.* 2018.
42. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2016;375(20):1946–60 **This clinical trial showed ustekinumab as an effective induction and maintenance agent for patients who previously failed anti-TNF α therapy or immunomodulators/glucocorticoids.**
43. Battat R, Kopylov U, Bessissow T, Bitton A, Cohen A, Jain A, et al. Association between ustekinumab trough concentrations and clinical, biomarker, and endoscopic outcomes in patients with Crohn's disease. *Clin Gastroenterol Hepatol.* 2017;15(9):1427–34 e2.
44. Papp K, Gottlieb AB, Naldi L, Pariser D, Ho V, Goyal K, et al. Safety surveillance for ustekinumab and other psoriasis treatments from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Drugs Dermatol.* 2015;14(7):706–14.
45. Dotan I, Ron Y, Yanai H, Becker S, Fishman S, Yahav L, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis.* 2014;20(12):2247–59.
46. Juncadella AC, Alame AM, Sands LR, Deshpande AR. Perianal Crohn's disease: a review. *Postgrad Med.* 2015;127(3):266–72.
47. Hukkinen M, Pakarinen MP, Piekkala M, Koivusalo A, Rintala R, Kolho KL. Treatment of complex perianal fistulas with seton and infliximab in adolescents with Crohn's disease. *J Crohns Colitis.* 2014;8(8):756–62.
48. Park EJ, Song KH, Baik SH, Park JJ, Kang J, Lee KY, et al. The efficacy of infliximab combined with surgical treatment of fistulizing perianal Crohn's disease: comparative analysis according to fistula subtypes. *Asian J Surg.* 2018;41(5):438–47.
49. Yarus AJ, Kanagala V, Stein DJ, Czul F, Quintero MA, Agrawal D, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther.* 2017;45(7):933–40.
50. Ji CC, Takano S. Clinical efficacy of adalimumab versus infliximab and the factors associated with recurrence or aggravation during treatment of anal fistulas in Crohn's disease. *Intest Res.* 2017;15(2):182–6.
51. Castano-Milla C, Chaparro M, Saro C, Barreiro-de Acosta M, Garcia-Albert AM, Bujanda L, et al. Effectiveness of adalimumab in perianal fistulas in Crohn's disease patients naive to anti-TNF therapy. *J Clin Gastroenterol.* 2015;49(1):34–40.
52. Fu YM, Chen M, Liao AJ. A meta-analysis of adalimumab for fistula in Crohn's disease. *Gastroenterol Res Pract.* 2017;2017:1745692.
53. West RL, van der Woude CJ, Hansen BE, Felt-Bersma RJ, van Tilburg AJ, Drapers JA, et al. Clinical and endosonographic effect of ciprofloxacin on the treatment of perianal fistulae in Crohn's disease with infliximab: a double-blind placebo-controlled study. *Aliment Pharmacol Ther.* 2004;20(11–12):1329–36.
54. Dewint P, Hansen BE, Verhey E, Oldenburg B, Hommes DW, Pierik M, et al. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). *Gut.* 2014;63(2):292–9.
55. Gold SL, Cohen-Mekelburg S, Schneider Y, Steinlauf A. Perianal fistulas in patients with Crohn's disease, part 1: current medical management. *Gastroenterol Hepatol (N Y).* 2018;14(8):470–81.
56. Feagan BG, Schwartz D, Danese S, Rubin DT, Lisssoos TW, Xu J, et al. Efficacy of vedolizumab in fistulizing Crohn's disease: exploratory analyses of data from GEMINI 2. *J Crohns Colitis.* 2018;12(5):621–6.
57. Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV Jr. Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis. *Gastroenterology.* 2015;148(1):64–76 e2 quiz e14.
58. Yamada A, Komaki Y, Patel N, Komaki F, Pekow J, Dalal S, et al. The use of vedolizumab in preventing postoperative recurrence of Crohn's disease. *Inflamm Bowel Dis.* 2018;24(3):502–9.
59. Hiraoka S, Takashima S, Kondo Y, Inokuchi T, Sugihara Y, Takahara M, et al. Efficacy of restarting anti-tumor necrosis factor alpha agents after surgery in patients with Crohn's disease. *Intest Res.* 2018;16(1):75–82.
60. Rutgeerts P, Geboes K, Vantrappen G, Beys J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology.* 1990;99(4):956–63.
61. Cohen-Mekelburg S, Schneider Y, Gold S, Scherl E, Steinlauf A. Risk stratification for prevention of recurrence of postoperative Crohn's disease. *Gastroenterol Hepatol (N Y).* 2017;13(11):651–8.
62. Catalan-Serra I, Brenna O. Immunotherapy in inflammatory bowel disease: novel and emerging treatments. *Hum Vaccin Immunother.* 2018:1–15.
63. White JR, Phillips F, Monaghan T, Fateen W, Samuel S, Ghosh S, et al. Review article: novel oral-targeted therapies in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2018;47(12):1610–22.