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Treatment Algorithms for Crohn's Disease

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Abstract
Background: Treatment of Crohn's disease (CD) patients is complex as therapy choices depend on a variety of factors, such as location and severity of inflammation, disease behavior (inflammatory, stricturing or penetrating) but also comorbidities, extra-intestinal manifestations, the patient's age, and previous therapies. Subsequently, the choice of treatment should be tailored to the individual patient. ***Summary:*** This article gives the reader therapy algorithms as a guide through different CD scenarios to support the physician's decision making. New compounds introduced in CD therapy in recent years justify such an update on standard approaches. Ustekinumab and vedolizumab and their positions within the treatment options are discussed. Fistulizing perianal disease and postoperative medical prophylaxis are depicted in separate chapters with own algorithms. ***Key Messages:*** In recent years, a variety of new drugs became available to treat patients with CD – especially those who are antitumor necrosis factor (TNF) experienced with ongoing inflammation. The definitive role of vedolizumab and ustekinumab is not yet fully clarified. However, with the advantage of good safety profiles over TNF-inhibitors, these drugs will be more frequently used in the near future, also as first-line biologicals, compared to TNF-inhibitors. Concerning treatment of fistulizing disease, the knowledge of the exact anatomy of the fistula is of major importance. An interdisciplinary discussion involving gastroenterologists, surgeons, and in some cases gynecologists may help to optimize the treatment plan. Regarding the postsurgical setting in CD patients, according to the very recent Cochrane Network meta-analysis, mesalazine should be at least positioned equivalent to thiopurines and TNF-inhibitors, as shown in our algorithm.

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) with relapsing and remitting symptoms that may lead to bowel damage and disability over time. There-

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fore, early diagnosis and adequate treatment should be achieved. Any part of the gastrointestinal tract can be affected by CD, the most common being the terminal ileum and the colon. The disease phenotype is described by the Montreal classification (Table 1) that categorizes CD patients according to their age at diagnosis, location of the disease, and disease behavior [1]. The prospectively validated Lemann Damage Score might better represent accumulating bowel damage over time [2, 3]. However, to date, there is no uniform reference standard to measure the integral disease burden in clinical practice. Indicators of severe disease course include smoking, sustained debilitating symptoms, repeated flare-ups, development of penetrating or stricturing lesions, need for repeated steroid treatment, and need for surgery [4]. Symptoms do not always correlate well with objective assessment such as endoscopy, cross-sectional imaging, or noninvasive biomarkers. Additionally, symptom scoring systems used in clinical trials (e.g., CD activity index) are not reliable measures of the underlying inflammation and consequently have almost no role in clinical practice. Fecal calprotectin may act as surrogate marker of luminal intestinal inflammation as it correlates well with endoscopic disease activity [5, 6]. Endoscopy can reliably visualize mucosal inflammation and grade disease activity but may be difficult to achieve in case of small-bowel involvement. However, CD is a transmural disease that may be more reliably assessed with cross-sectional imaging (computed tomography, magnetic resonance imaging) or ultrasonography (US) [7, 8]. In clinical trials, patients are stratified into mild, moderate, or severe disease activity at a certain point in time with clinical scoring systems, for example, CD activity index. However, these scores do not assess overall disease burden and the patient's risk profile. Clearly, there is a need for validated indices of severity [9].

Not only the abovementioned disease parameters but also the patient's age, relevant comorbidities, possible extra-intestinal manifestations, previous therapies, and the presence of complicated disease risk factors [4, 10] (Table 2) impact the individual therapeutic decision. Patient's perception to treatment and also to the disease is one of the most important aspects to achieve good treatment adherence [11]. Thus, the possibility to simplify CD treatment is limited. Nevertheless, more general recommendations certainly are possible and can be summarized in respective algorithms for CD treatment that support the physician's decision to treat the patient as best as possible. The algorithms presented in this manuscript should point out the practicability of this review. They are based on the guidelines of the European Crohn's and Colitis Organization (ECCO) and include also their very recently published updates (January 2020) [12–14] and are expert based opinions (without voting). A systematic review of the literature was not repeated (but done for the ECCO guidelines). Based on the current literature, we aimed to position recently approved drugs such as ustekinumab and vedolizumab within the therapy algorithm.

Table 1. Montreal classification [1]

Age at diagnosis
A1 below 16 years
A2 between 17 and 40 years
A3 above 40 years
Location
L1 ileal
L2 colonic
L3 ileocolonic
L4 isolated upper disease*
Behavior
B1 nonstricturing, nonpenetrating
B2 stricturing
B3 penetrating
p perianal disease modifier†

The Montreal classification characterizes the phenotype of CD according to the patient's age at diagnosis, the location of inflammation within the gastrointestinal tract, and also the disease behavior.

* L4 is a modifier that can be added to L1–L3 when upper gastrointestinal disease is coexistent.

† "p" is added to B1–B3 when concomitant perianal disease is present.

A, age at diagnosis; L, location of disease; B, behavior of disease; p, perianal disease; CD, Crohn's disease.

Table 2. Indicators for severe disease/disease progression [4, 10]

Indicator
Young age at diagnosis
Corticoid steroids necessary at time of diagnosis
Early stricturing or penetrating disease (B2 and/or B3[a])
Ileal or ileocolonic disease location (L1 or L3[a])
Rectal disease
Severe upper gastrointestinal disease (L4[a])
Perianal disease
Severe endoscopic lesions
Smoking
Positive antimicrobial markers
NOD2-mutation (risk for ileal disease/risk of surgery)

[a] According to the Montreal classification (Table 1).

This table shows a list of indicators that are associated with a severe disease course and disease progression in patients with CD.

CD, Crohn's disease; NOD2, nucleotide-binding oligomerization domain-containing protein 2.

Table 3. List of medications for CD [15]

Agent	Dosage
5-Aminosalicylic acid	
Mesalazine	Above 2.4 g/day
Corticosteroids	
Budesonide	9 mg/day
Prednisone	0.75–1 mg/kg body weight/day
Immunosuppressive agents	
AZA	2–2.5 (max. 3) mg/kg body weight/day
6-MP	1–1.5 mg/kg body weight/day
MTX	10–25 mg per week + 5 mg folic acid
Antibiotics	
Metronidazol	1,000–1,500 mg/day
Ciprofloxacin	1,000 mg/day
Biologicals	
Adalimumab (Humira®/Hyrimoz®/Amgevita®)	Subcutaneous injection Week 0: 160 mg Week 2: 80 mg Week 4: 40 mg Then, every other 2 weeks: 40 mg
Infliximab (Remicade®/Inflectra®/Remsima®)	Infusion over 30–90 min Week 0: 5 mg/kg Week 2: 5 mg/kg Week 6: 5 mg/kg Then, every 8 weeks: 5 mg/kg
Certolizumab pegol* (Cimzia®)	Subcutaneous injection Week 0: 400 mg Week 2: 400 mg Week 4: 400 mg Then, every 4 weeks: 400 mg
Vedolizumab (Entyvio®)	Infusion over 30 min Week 0: 300 mg Week 2: 300 mg Week 6: 300 mg Then, every 8 weeks: 300 mg
Ustekinumab (Stelara®)	Infusion week 0 ≤55 kg 260 mg 55 to <85 kg 390 mg >85 kg 520 mg Then 90 mg subcutaneous injection after 8 weeks then every other 12 (or 8) weeks

* Certolizumab pegol is only approved in the United States and in Switzerland.

This table gives an overview of currently available drugs for the treatment of CD, grouped in mesalazine, corticosteroids, immunosuppressives, antibiotics (if indicated), and various biologicals. Common dosages are given. Biologicals which are not yet approved are not considered in this publication.

CD, Crohn's disease; AZA, azathioprine; 6-MP, 6-mercaptopurine; MTX, methotrexate.

Medical Therapy for CD

Historically, treatment of CD has relied mainly on corticosteroids and immunosuppressive medication with thiopurines (azathioprine [AZA]/5-mercaptopurin [5-MP]) or methotrexate (MTX; Table 3). Though the introduction of corticosteroids achieved reduction of mortality in CD patients, this treatment is associated with many well-known undesired adverse effects and therefore not useful for long-term treatment. Two decades ago, the treatment armentarium was extended by infliximab, the first tumor necrosis factor (TNF)-inhibitor, especially for

patients with severe disease course and those who were refractory or intolerant to immunosuppressives [16]. However, therapy with TNF-inhibitors is still challenging as 20–40% of patients have primary nonresponse to the drug and 23–46% experience secondary loss of response over time [17]. In addition, approximately 5% of patients suffer from anti-TNF induced psoriasis [18] or lupus-like syndrome. Challenges also remain in treating elderlies who have significant comorbidities (e.g., heart failure) or patients with a history of malignancy.

Over the last couple of years, a number of new drugs have been developed and approved based either on inhibition of immune cell trafficking or on inhibition of cytokine signaling [19–22]. Vedolizumab, a monoclonal antibody directed against α4β7 integrin, has been approved for the treatment of patients with moderate-to-severe UC or CD who have inadequate response, loss of response or intolerance to conventional therapy with corticosteroids, immunosuppressives, or anti-TNF therapy. It is effective in the induction and maintenance of remission in refractory and luminal CD [23]. In real-world CD cohorts, clinical remission and response rates after induction therapy (usually evaluated at week 14) ranged from 24–36% to 49–64%, respectively, [24–27]. Vedolizumab prevents circulating immune cells from homing to the mucosa and is gut-selective through interactions with mucosal adhesion molecules. This may be a specific advantage in long-term safety [28] and may also explain the longer period of time to induce remission (12–16 weeks), compared to TNF-inhibitors. Therefore, vedolizumab is not the ideal choice in patients with severe CD who are acutely ill where fast response to treatment is needed. In the latest ECCO guideline [13], the position of vedolizumab is adapted as it is now also clearly recommended to be used for induction and remission in patients with moderate to severe CD with inadequate response to conventional therapy with immunosuppressives. In other words, it is recommended as a first-line biological. However, the ECCO guideline does not discuss in detail which patients should be commenced on vedolizumab or anti-TNF inhibitors. In our opinion, vedolizumab is suitable as a first choice biological in elderlies with comorbidities and elevated risk of infection and patients with history of malignancy, where safety is of particular concern.

Ustekinumab is a monoclonal IgG1 antibody against the p40 subunit of interleukin-12 (IL-12) and IL-23 that targets T-helper cell pathways which promote the accumulation of inflammatory cells within the intestine. It was approved for the treatment of patients with moderate-to-severe CD who have failed or were intolerant to treatment with corticosteroids, immunosuppressives, or anti-TNF therapy. Ustekinumab has shown to be effective in inducing and maintaining remission [29, 30], with higher response rates in TNF-naïve than in TNF-experienced patients (54–58% vs. 34%, respectively) [31]. In the updated ECCO guideline [13], ustekinumab has an expanded position within the approved biologicals as it can also be used as a first-line biological – such as vedolizumab. Again, the ECCO guideline does not give recommendation where to prefer ustekinumab over TNF-inhibitors or over vedolizumab as first-line option. In our opinion, ustekinumab has its particular place as first-line biological, especially in patients with psoriasis and CD. Furthermore, this drug is a suitable option in patients who have developed severe TNF-induced psoriasiform disease [18].

However, at least to date, TNF-inhibitors are less expensive (especially since biosimilars are available), and the clinical experience with TNF-inhibitors is much greater compared to the new biologicals. The safety profile of both ustekinumab and vedolizumab seems favorable, but long-term safety still needs to be confirmed in postmarketing studies.

Therapy Algorithm for Endoluminal CD

The therapy algorithm for endoluminal CD (Fig. 1) guides the reader through different endoluminal CD scenarios. Ustekinumab and vedolizumab and their positions within the treatment options are discussed.

According to the ECCO guidelines [12, 13], budesonide (initially 9 mg) orally is the best treatment option for mildly active localized ileo-cecal disease to induce remission which can be achieved in up to 60% of patients after a therapy course over 8 weeks [37, 38]. For moderately active localized ileo-cecal disease, either budesonide or systemic oral corticosteroids are recommended. Usually, budesonide 9 mg daily is somewhat less effective than oral systemic steroids (relative risk [RR] 0.85, 95% CI 0.75–0.97), especially in severe disease (RR 0.52, 95% CI 0.28–0.95); however, oral budesonide is associated with less side effects (RR 0.64, 95% CI 0.54–0.76) [39, 40]. Systemic corticosteroids are suitable in colonic and small bowel CD to induce remission [12].

For decades, mesalazine has been used to achieve remission in CD. Still nowadays, mesalazine is often prescribed; up to one-third of patients in the Epi-IBD cohort was treated with mesalazine [41]. However, the latest ECCO guidelines [13] suggest not to use mesalazine (or sulphasalazine) for CD treatment due to lack of support-

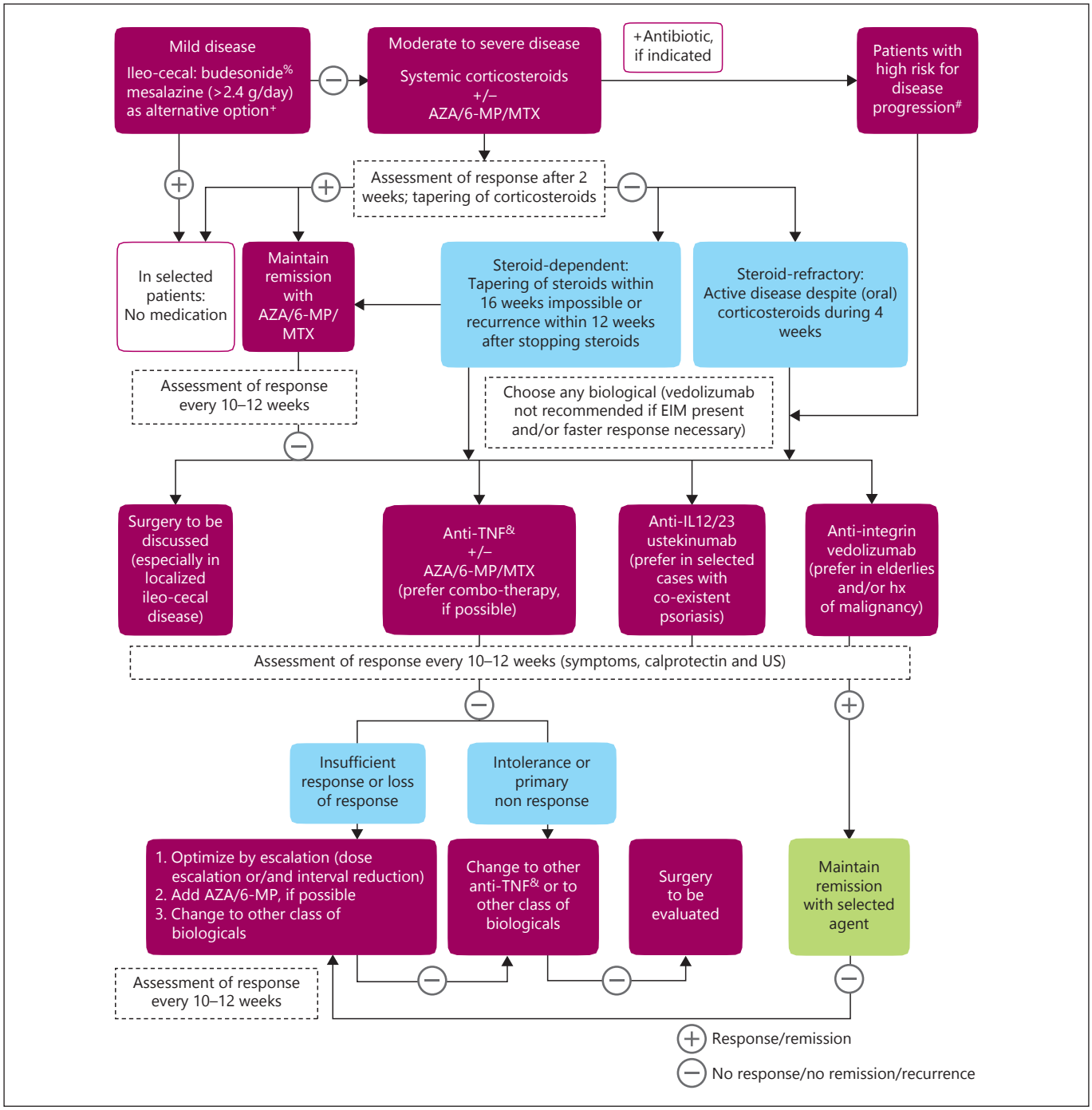

Fig. 1. Therapy algorithm for endoluminal CD [12, 13, 23, 29, 30, 32–36]. To keep this algorithm as simple as possible and for reasons of repetition and similarity, location and extent of inflammation (localized ileo-cecal, colonic, and extensive small bowel disease) are not specifically represented. Also, for reasons of simplicity, the severity of inflammation (mild/moderately severe/severe) is not differentiated. However, high-risk situation for progressive disease and steroid-dependent/steroid-refractory inflammation are discussed as separate entities. Surgery as a therapeutic option in endoluminal CD treatment is integrated in the algorithm, where indicated. + For more details, see main text. % Budesonide: cortiment multi matrix is not approved for treatment of CD. # Table 1: indicators for severe disease/disease progression. & Anti-TNF: infliximab and its biosimilars (Remicade®/Inflectra®/Remsima®); Adalimumab and its biosimilars (Humira®/Hyrimoz®/Amgevita®); CertolizumabPegol (Cimzia®), only approved in Switzerland and USA. CD, Crohn's disease; AZA, azathioprine; IL, interleukin; 6-MP, 6-mercaptopurine; MTX, methotrexate; TNF, tumor necrosis factor; EIM, extraintestinal manifestations; US, ultrasonography.

ing data. The working group performed a meta-analysis of 7 randomised trials comparing mesalazine (5 studies) and sulphasalazine (2 studies), published in the supplements [13]. The Cochrane Network meta-analyses are inconsistent: A recent Cochrane Network meta-analysis by Coward et al. [42] demonstrated a significant benefit for high-dose mesalazine (above 2.4 g daily) over placebo (OR 2.29, 95% CI 1.58–3.33). However, another Network meta-analysis could not confirm such a dose effect [43]. Indeed, it has to be mentioned that the ECCO recommendation is stated as "weak" and based only on moderate evidence. Furthermore, a risk-benefit analysis has not been performed. According to the meta-analysis, mesalazine is well tolerated [13]. In our opinion, mesalazine may still be a treatment option and may be offered to patients who refuse repetitive steroids or do not want to escalate therapy toward immunosuppressives or biologicals.

Local mesalazine (rectal foam/enema) in left-sided CD colitis is not recommended by the ECCO guidelines, due to lack of convincing data [12, 13]. This treatment has not been studied in randomized controlled studies. To date, budesonide multi matrix with a colonic delivery technology is not (yet) approved for CD.

Generally, the response of induction therapy should be clinically assessed after 2 weeks. Usually, tapering of corticosteroids starts after 2 weeks. In selected cases (first flare and mild localized disease), no further therapy may be considered (ECCO statement 5 C; [12]). A population-based study investigated the outcome of first steroid treatment in CD patients and revealed that 80% of the patients had a primary response within 30 days of therapy (48% with complete remission; 32% with partial response). Of those, 55% had prolonged response within 1 year. However, 45% had either a course of relapses or stayed steroid dependent [44]. Therefore, in around half of the patients, a concomitant therapy with either immunosuppressive agents (AZA/6-MP or MTX) or biological treatment must be considered as a steroid-sparing concept. Patients with several indicators predictive for a severe disease course (Table 2) should be early commenced on a biological treatment. When TNF-inhibitors have become available, early start of anti-TNF therapy in these patients increasingly became common practice, given the fact that continued treatment with either infliximab or adalimumab has been associated with a substantial reduction in hospitalisation (with adalimumab every other week: 52 and 48% relative reductions in 12-month risk of all-cause and CD-related hospitalisation, respectively) and surgery for CD (major surgery rate in the adalimumab every other week arm almost 7 times lower than that in the placebo arm [$p < 0.05$]) [45, 46]. The literature shows that combined treatment with infliximab and AZA (at least 6 months) is more effective than infliximab alone to induce and maintain remission without steroids (SONIC trial) [46, 47]. Of course, the treating physician has to bear in mind the patient's individual situation including safety profile. However, it must be stated that a significant reduction of surgery rates up to 40% has also been shown for thiopurines [48].

Generally, treatment in patients with extensive small bowel disease (defined as involvement of >100 cm small bowel) should be more aggressive [49] and TNF-inhibitors should be early started, also in combination with immunosuppressives, if possible [50]. Early start of anti-TNF therapy is more effective in extensive disease than a late start [51, 52]. The CHARM trial with adalimumab could show that 60% of patients with CD <2 years of duration reached clinical remission, compared to 40% ($p < 0.05$) of patients who had a longer duration of disease [51].

As mentioned, recently, new biologicals became available, such as the anti-α4β7-integrin monoclonal antibody vedolizumab, and the IL-12/23 p40 antibody ustekinumab. The updated ECCO guideline [13] recommends them to be used also as first-choice biologicals. Vedolizumab (and also ustekinumab) may be preferred over TNF-inhibitors in elderly patients or in patients with history of malignancy, as these drugs have a very good safety profile. However, one needs to bear in mind that vedolizumab is not effective against extraintestinal manifestations and is also not suitable when a fast response should be expected. Furthermore, ustekinumab is the preferred biological agent in patients with coexistent psoriasis (see above).

Certainly, it is important to recognize patients who are steroid-dependent (defined as relapse within 12 weeks during tapering or tapering within 16 weeks impossible) or refractory to steroids (defined as nonresponse within 4 weeks). In those patients, biological therapy should be initiated [53].

Patients with early relapses and frequent flares during immunosuppressive therapy should be commenced on biological treatment (see below). Alternatively, surgical resection can be discussed or evaluated, especially in localized disease and in those patients who still have active inflammation despite experience with all TNF-inhibitors and other biologicals.

Monitoring of patients with CD is important and is recommended by the ECCO guidelines [8]. In patients who reached clinical and biochemical remission, monitoring aims at early flare recognition [8]. According to

the ECCO guidelines fecal calprotectin can be used to detect relapse before clinical symptoms occur. The monitoring time interval should be between 3 and 6 months depending upon duration of remission and current therapy [8]. Other than in North America, in Europe, especially in Germany and Switzerland, monitoring of IBD patients with US is much more common and frequently performed by many gastroenterologists in clinical practice. A German prospective multicenter study found that bowel US can be used to monitor disease activity in patients with active CD [54]. This method seems to be a useful follow-up method to evaluate early transmural changes in disease activity, in response to medical therapy [54]. Hence, US is implemented as one of the monitoring instruments in our therapy algorithm (Fig. 1).

In case of inadequate response or loss of response, different options can be chosen to optimize the treatment: Serum trough levels of biologicals, especially of TNF-inhibitors, can be monitored and dosage adapted if required, also called therapeutic drug monitoring (TDM). It is also possible to optimize the TNF-inhibitor therapy based on clinical judgement only, without measuring drug trough levels or anti-TNF antibodies. The updated ECCO guideline commented on this aspect that there is currently no evidence to recommend for or against the use of TDM to improve the clinical outcome [13]. This statement is based on the only randomized controlled, multicenter study with 69 patients that showed no significant difference in improving clinical response between the TDM-group and the symptom-based group (57.6 vs. 52.8%; RR 1.09, 95% CI 0.71–1.67; $p = 0.81$) [55]. Overall, despite the limited evidence, TDM might bring a cost-saving benefit [56]. Adding AZA/5-MP or MTX could be another step to increase efficacy of TNF-inhibitors, especially in patients treated with infliximab. In case of antibody formation against the TNF-inhibitor which was used (e.g., infliximab), a switch to another one (e.g., adalimumab or certolizumab pegol; certolizumab pegol approved for CD in Switzerland and United States) would be recommended (switch within class).

In patients with primary nonresponse despite adequate dosage or intolerance to the drug, an alternative TNF-inhibitor or another class of biologicals (vedolizumab or ustekinumab) must be selected. The preference should be given to change the mechanism of action.

Especially in localized ileo-cecal disease, surgery is also a reasonable option in patients who deny medical treatment options (due to any reason) or in those who are not compliant toward medical therapy.

Esophageal and gastroduodenal disease: According to the ECCO statement 5 H, mild esophageal or gastroduodenal disease may be treated with proton pump inhibitors only [12]. However, it needs to be mentioned that CD in the proximal gut is associated with a worse prognosis [57]. Therefore, in general, more aggressive treatment should be recommended. Evidence-based therapy is mainly based on case series [58, 59]. Many clinicians add a proton pump inhibitor to conventional induction therapy and have a low threshold for starting anti-TNF therapy than for disease elsewhere.

Therapy Algorithm for Fistulizing Disease

The knowledge of the exact anatomy of the fistula is of major importance in order to plan the treatment. An interdisciplinary discussion involving gastroenterologists, surgeons, and in some cases gynecologists may help to optimize the treatment plan.

The proper assessment of fistulae by magnetic resonance imaging, endosonography, and exploration under anesthesia allows to differentiate between simple perianal fistulae and complex fistulae according to Sandborn et al. [60] (Fig. 2). Complicated fistulae can be considered as a risk factor for poor prognosis and should therefore be aggressively treated. These complex fistulae are: high (high means involving >2/3 of the external sphincter) intersphincteric, high transsphincteric, suprasphincteric, and extrasphincteric, may have multiple openings and may be associated with an abscess, proctitis, rectal stricture, or may be connected with the bladder or vagina [60]. Any anterior fistula in women is generally considered complex due to potential genital complications [61]. In contrast, simple fistulae are low fistulae that involve superficial tissue and include subcutaneous and intersphincteric and intrasphincteric fistulae that remain below the dentate line, have a single opening, and are not associated with perianal complications [60, 61].

It is compulsory to rule out a perianal abscess first; perianal pain is almost always associated with an abscess. If suspected or already detected, urgent exploration under anesthesia combined with drainage performed by a colorectal surgeon is the treatment of choice to prevent the destruction of undrained local sepsis. Furthermore, procto-sigmoidoscopy should be performed to search for active luminal disease. If detected, it must be treated achieving and maintaining remission [32].

An asymptomatic simple fistula does not need treatment. When symptomatic, a simple fistula may be treated

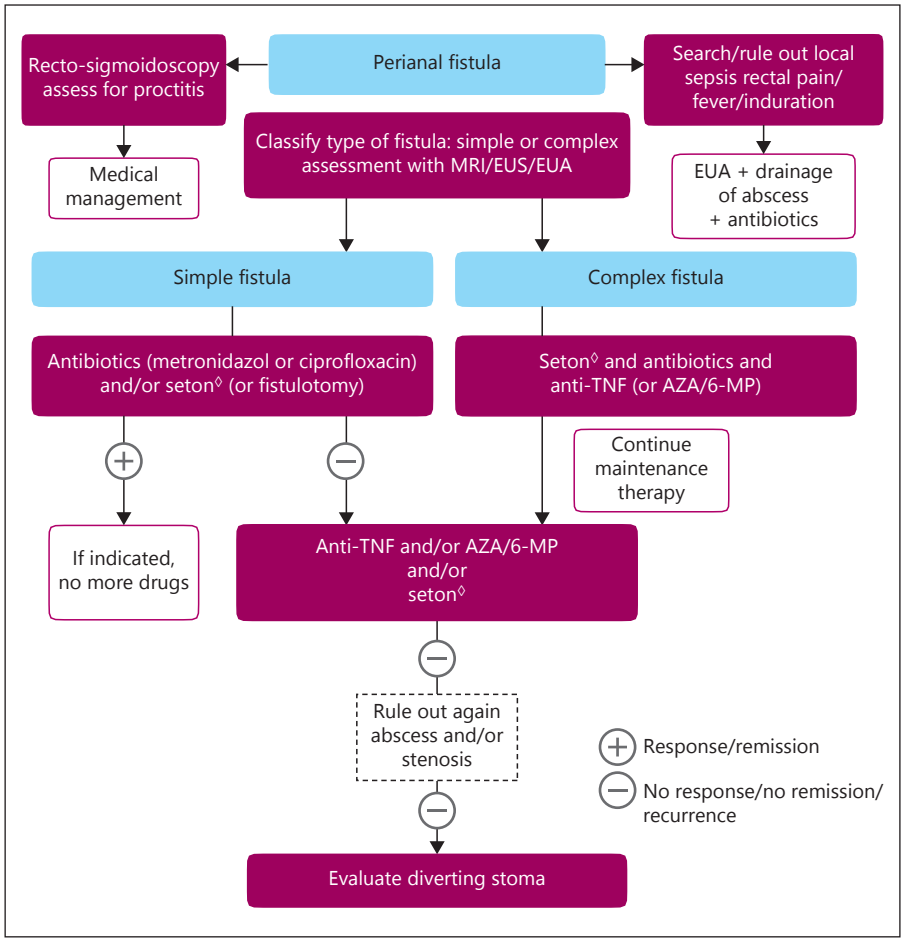

Fig. 2. Management of fistulizing perianal disease [10, 12, 14, 32, 33, 36, 61]. Simple fistulae: Low fistulae that involve superficial tissue and include subcutaneous and intersphincteric and intrasphincteric fistulae that remain below the dentate line, have a single opening and are not associated with perianal complications. Complex fistulae: are high (high means involving >2/3 of the external sphincter) intersphincteric, high transsphincteric, suprasphincteric, and extrasphincteric, may have multiple openings, and may be associated with an abscess, proctitis, rectal stricture or may be connected with the bladder or vagina. ◊ Seton: Seton, not cutting. AZA, azathioprine; EUA, examination under anesthesia; EUS, endoscopic ultrasonography; 6-MP, 6-mercaptopurine; MRI, magnetic resonance imaging; TNF, tumor necrosis factor.

conservatively (with antibiotics) and/or surgically by fistulotomy (seton) after abscess formation has been ruled out. In case of nonresponse, anti-inflammatory therapy (either with immunosuppressives or with TNF-inhibitors) should be added to gain healing [32].

Complex fistulae should be primarily treated with setons and/or antibiotics and a biological treatment (usually a TNF-inhibitor) [14]. A systematic review of heterogeneous retrospective studies revealed that the combination of surgical and medical therapy may have a beneficial healing effect of perianal fistulae compared with surgery or medical therapy alone [59, 62]. To date, randomized controlled trials or prospective studies comparing anti-TNF treatment alone versus anti-TNF and surgery combined to treat complex perianal CD fistulae are not available [14]. If the treatment plan aims for fistula closure, the seton must be removed, often toward the end of the induction phase of the TNF-inhibitor [63]. However, optimal timing of removal is unknown. One option is to keep loose setons permanently in situ to control local sepsis and reduce symptoms, although they may need to be replaced at some time. Loose setons can also serve as a bridge between medical therapy and the definitive surgical treatment. Cutting setons are not recommended in the treatment of perianal CD as they are a method of fistulotomy implicating a risk of sphincter injury [63].

Fistulectomy should only be used in selected cases due to the risk of fecal incontinence [32]. In severe therapy-refractory fistulizing disease, fecal diversion with colostomy or ileostomy may be evaluated. Often, this option is not easy to discuss with the individual patient. However, sometimes it is the only way to prevent further structural damage and to increase the healing of complex fistulae. It has to be stated that the fistula healing rate and stoma closure rate are limited [14]. For details concerning definitive surgical treatments, it is referred to Gecse et al. [63], Adegbola et al. [64], and the updated ECCO guideline [14].

Several medications are used for the treatment of fistulae. Antibiotics such as metronidazole and ciprofloxacin

seem to be helpful and are frequently used to treat the infectious complications of fistulizing disease. Only small studies are available, most of them showing that the therapeutic effect is limited to the time of antibiotic treatment. Antibiotics are useful to alleviate symptoms, but usually, they do not induce complete healing in complex fistulae [32]. According to the updated ECCO guideline, antibiotics have no role as monotherapy in closing fistulae [13]. Bacteria show increasing rates of resistance to ciprofloxacin; therefore this medication will have limited use in the future [65]. Steroids have not shown to play a role in the treatment of fistulae; they even may enhance septic complications. Thiopurines have been used in the treatment of fistula; however, there are limited data. A meta-analysis of 5 randomized, placebo-controlled trials which assessed perianal fistula closure only as a secondary endpoint revealed that thiopurines were effective in inducing fistula closure (OR of response 4.44) [66]. However, a substantial number of patients needed to stop this treatment due to side effects [66]. Due to lack of data, the updated ECCO guideline suggested against using thiopurine monotherapy for fistula closure [13].

TNF-inhibitors are the medical mainstay in fistula treatment. The data from Present et al. [67] showed a significant closure and response rate to infliximab. However, it needs to be mentioned that the study endpoints were somewhat imprecise. The ECCO working groups performed a meta-analysis of the existing data showing that infliximab was clearly effective in inducing (RR 3.57, 95% CI 1.38–9.25) and maintaining (RR 1.79, 95% CI 1.10–2.92) clinical fistula healing [13]. The ECCO guideline clearly recommends infliximab as first-line biological for treating complex fistulizing CD [13]. Also adalimumab – although less strongly – is suggested to use for this indication by the ECCO guideline [13]. Adalimumab has shown to be effective in fistula closure in about 40% of cases [68]. In a small pediatric cohort, the fistula closure rate was 44% [69]. The combined treatment with adalimumab and ciprofloxacin seems to be superior to an anti-TNF treatment only; however, the positive effect is limited to the time the antibiotic is taken [70]. Adalimumab should be used in patients with previous infliximab failure as shown by the CHOICE trial [71]. Compared to the former ECCO guideline, the updated one does not support a decision for or against the use of thiopurines combined with TNF-inhibitors to enhance the effect of anti-TNF in complex fistulizing disease [13]. A meta-analysis in 2015 based on 11 randomized controlled trials revealed no apparent benefit from the above combined therapy as regards partial (OR 1.25, 95% CI 0.84–1.88) or complete fistula closure (OR 1.1, 95% CI 0.68–1.78) [72].

To date, there are only few data available regarding the efficacy of ustekinumab in perianal CD. However, a French multi-center observational study (Bio-LAP) showed that ustekinumab appears as a fairly effective therapeutic option in perianal refractory CD [70]. Among patients with setons at the time ustekinumab was started, successful seton ablation during follow-up was possible in 29/88 (33%) [73]. In a recent systematic review and meta-analysis of 27 controlled trials, a moderate-quality evidence was found to support the efficacy of ustekinumab to induce fistula remission (RR 1.77, 95% CI 0.93–3.37) [74]. However, no difference was found for maintenance of remission, compared to placebo. Currently, the updated ECCO guideline stated that the evidence for ustekinumab is insufficient for fistula healing [13]. For vedolizumab, only low-quality evidence was found in this meta-analysis [74]. Clearly, more studies are needed to define the role of ustekinumab and also vedolizumab related to other biological therapies for the management of refractory perianal fistulizing CD. However, these biologicals may be used in TNF-refractory patients, or where TNF-inhibitors are contraindicated and luminal activity is also ongoing.

Recently, several studies about fistula curettage and mesenchymal stem cell therapy have been published and analyzed in a recent recent systematic review and meta-analyis (23 studies with 696 patients) [75], showing significant results concerning fistula closure (overall 80% success rate). However, the 4 randomized controlled trials (483 patients) revealed a closure rate of 64% (vs. 37% in the control arm). The uncontrolled studies in this analysis most likely lead to overestimate the efficacy of this novel therapy. However, safety data are good and the relapse rate is low. This costly treatment needs to be evaluated in clinical practice and should be currently limited to refractory difficult to treat cases. Overall, complex perianal fistulizing disease remains a challenging and limiting condition to treat. Further work is needed to optimize management in this special group of CD patients.

Algorithm for Postsurgical Prophylaxis

Unfortunately, for the majority of CD patients, surgery is not curative. The cumulative rate of symptomatic (clinical) recurrence is high (at 3 years approximately 50%) [76]. Endoscopic assessment of the neoterminal ileum (ileocolonoscopy) is strongly recommended as gold standard for the diagnosis of postoperative endoscopic recurrence by the ECCO guidelines within the first year after surgery (EL2 [32]), based on the modified Rutgeert-Score

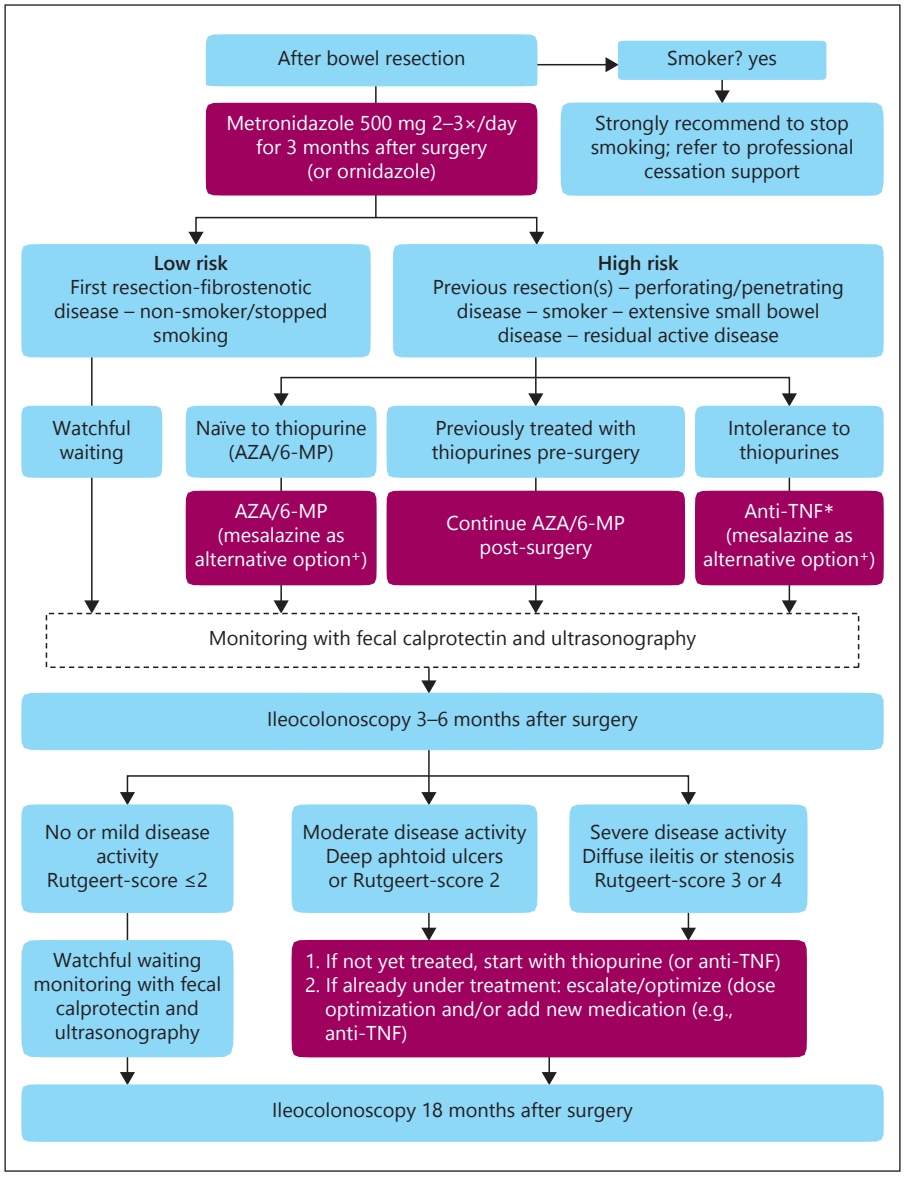

Fig. 3. Management of postoperative CD [12, 32, 33, 36, 79–81, 89]. Prevention of recurrence is a relevant aspect of the postsurgical management in CD patients. A personalized risk stratification with tailored therapy is of relevance. Furthermore, the status of previous therapy and the patient's attitude toward medical treatment should be considered. * Prefer adalimuab [89]; + for more details, see main text. AZA, azathioprine; 6-MP, 6-mercaptopurine; TNF, tumor necrosis factor.

[76]. The endoscopic recurrence rate is even higher and predicts future clinical relapse. A meta-analysis showed an endoscopic recurrence rate of 58% (95% CI 51–65%) 1 year (median) after surgery in the placebo groups of postoperative maintenance trials [77]. Therefore, prevention of recurrence is an important part of the postsurgical management in CD patients. In this setting, a personalized risk stratification with tailored therapy is eligible. However, despite a number of guidelines including the ECCO, the British Society of Gastroenterology, and American College of Gastroenterology guidelines [32, 36, 78], a robust algorithm for the prevention and treatment of postoperative recurrence is not yet established. The algorithm presented in this publication is based on the available literature and our opinion and should help the reader as a recommendation in daily practice (Fig. 3).

A general prophylaxis with metronidazole (500 mg 2–3 x/day; or ornidazole) limited to 3 months is easy to perform. Despite limited data and only moderate tolerance, this prophylaxis commenced directly after surgery is still recommended by the ECCO guidelines [32] and also by the recent consensus guidelines of the British Society of Gastroenterology [36]. Endoscopic recurrence at 1 year was reduced by a 3-month metronidazole course, but not sustained beyond 12 months [80]. Decision making in the postoperative setting is based on several factors,

mainly on the individual risk factors leading to the constellation of either "low risk" or "high risk" (Fig. 3). Smoking as the only modifiable risk factor is well replicated and associated with a 2-fold and a 2.5-fold increase in clinical and endoscopic recurrence, respectively, after surgery among smokers versus nonsmokers [82]. It has been shown that smoking cessation is correlated with a decreased risk of postoperative recurrence [83, 84]. It is of note that each smoking patient should be counseled about the importance to quit smoking. Professional cessation support (counseling, pharmacotherapy, or nicotine replacement therapy) should be offered with efforts (Fig. 3).

In patients with low risk (first resection, fibrostenotic disease, and nonsmoker), no further medical prophylaxis may be opted. In high-risk situations (≥1 previous resection, perforating disease, and smoker-status), prophylaxis with TNF-inhibitors and/or immunosuppressives (thiopurines) are recommended as agents of choice by both, the ECCO and the American Gastroenterological Association guidelines [32, 85]. A more precise recommendation for the prevention of postoperative CD recurrence is missing in the guidelines. In 2014, a Cochrane review revealed that thiopurines had lower clinical relapse rates compared with placebo (RR 0.74, 95% CI 0.58–0.94), but with low-quality evidence [86]. However, a large placebo-controlled trial called TOPPIC (240 patients randomized to 6-MP at 1 mg/kg/day versus placebo after surgery, follow-up for 3 years) showed a small but not significant effect of treatment (clinical recurrence rate: 13% in the 6-MP group versus 23% in the placebo group, requiring medical or surgical intervention [$p = 0.07$]) [87]. Interestingly, 60% of patients in the 6-MP group had subtherapeutic levels at week 49. A subgroup analysis revealed that 6-MP had a significant effect in reducing clinical recurrence in smokers compared with nonsmokers (p interaction = 0.018). Regarding TNF-inhibitors, the largest randomized placebo-controlled trial (called PREVENT; 297 patients with ileocolic resection and ileocolonic anastomosis and increased risk of recurrence, infliximab 8 weekly versus placebo) confirmed that TNF-inhibitors were effective to prevent postoperative recurrence [88]. Although endoscopic recurrence was significantly lower (22%) in the infliximab group than in the placebo group (51%; $p < 0.001$), the primary endpoint of this study, defined as clinical recurrence up to week 76, was not met (recurrence rates 13% for the infliximab group and 20% for the placebo group; $p = 0.097$).

Obviously, the newest Cochrane Network meta-analysis published in September 2019 [89] puts current guideline recommendations on postoperative medical management into a new perspective. These data reveal insufficient evidence to determine which treatment is safest or most effective in preventing clinical and endoscopic relapse because of very low certainty of evidence [89]. Partially, these new data conflict with recommendations of the current guidelines [32]. For example, the ECCO guidelines recommend thiopurines or TNF-inhibitors as drug of choice to prevent postsurgical recurrence (EL2 [32]). High-dose mesalazine is only declared as an option for patients with an isolated ileal resection (EL2 [32]). In contrast, according to the new network meta-analysis, there is only for mesalazine and adalimumab some evidence to prevent clinical relapse [89]. Based on these data, mesalazine should be at least positioned equivalent to thiopurines and TNF-inhibitors as shown in our algorithm (Fig. 3).

The choice of medical prophylaxis should also consider the patient's attitude toward medical treatment. Even in a high-risk situation, some patients prefer not to take medication after surgery, especially when they are feeling well or they fear possible side effects of medications. Compared to thiopurines and TNF-inhibitors, mesalazine has a better overall safety profile which might be an argument to think of it. Alternatively, patients who are naïve to thiopurins can be commenced on AZA (or 6-MP). In patients who had been preoperatively already on thiopurins, thiopurins are continued. In case of thiopurine intolerance, anti-TNF therapy is commenced (Fig. 3). According to the new Cochrane Network meta-analysis, adalimumab will probably have a stronger position among the availale TNF-inhibitors [89].

In case the first postoperative endoscopic assessment shows no or mild inflammation (Rutgeert-Score <2), prophylaxis may be stopped. In cases of relevant mucosal inflammation (Rutgeerts 2 or above), escalation needs to be considered: Either starting medical treatment or switching from mesalazine to thiopurines or from thiopurines to TNF-inhibitors or escalating the dosage of TNF-inhibitors. The strategy to use endoscopy in the decision making is mainly based on the data of the POCER trial, a large randomized clinical trial which provided evidence that endoscopy can guide postoperative CD management to lower the risk of recurrence [79]. The POCER trial compared an active care model using endoscopic assessment at 6 months postoperatively with standard care (no colonoscopy at 6 months). All patients received metronidazole for 3 months postoperatively; high-risk patients received thiopurines (or adalimumab in case of purine intolerance). In the case of 6-month endoscopic recurrence treatment step-up in the active care group was performed: to thiopurine, fortnightly adalimumab with thiopurine, or weekly adalimumab, respectively. At 18 months endoscopic recurrence was 49% in the active

group versus 67% in the standard care group ($p = 0.03$) and clinical recurrence was 27 and 40%, respectively ($p = 0.08$) [79]. Thirty-nine percent of patients in the active care group had a step up in treatment based on the results of the colonoscopy at 6 months. Out of this patient group, 38% had achieved endoscopic remission at the next colonoscopy at 18 months. Furthermore, it is of note that a relevant portion (41%) of patients in endoscopic remission at 6 months was documented with endoscopic recurrence just 1 year later (at 18 months). Therefore, continued monitoring is important. In clinical practice, endoscopic assessment may be repeated 18 months after surgery. In general, regular monitoring with US and fecal calprotectin may be recommended.

Closing Remarks and View on Emerging Therapies in CD

In recent years, a variety of new drugs became available to treat patients with CD – especially those who are anti-TNF experienced with ongoing inflammation. Meanwhile, vedolizumab and ustekinumab are more clearly positioned not only as second-line but also as first-line biologicals besides TNF-inhibitors. With the advantage of good safety profiles (compared to TNF-inhibitors), these drugs will be more frequently used in the near future. Certainly, it will be also a discussion whether vedolizumab will be a better option than AZA prior to anti-TNF treatment, especially in elderly male patients with higher risk of lymphoma. However, this would negatively impact the health costs in IBD-patients.

Certainly, the therapy algorithm of CD depicted in this article will be complemented by a variety of further emerging drugs which might be approved in the near future, such as risankizumab and mirikizumab, anti-p19 antibodies with selective activity against IL-23, and Janus kinase inhibitors, such filgotinib and upadacitinib as oral selective Janus kinase-1 inhibitors. Currently, large trials are ongoing.

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Statement of Ethics

Ethical approval or written informed consent was not required as this article is a review.

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