Chapter 15
Medical Therapy in Stricturing Inflammatory Bowel Diseases

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Abstract Both, Crohn's Disease (CD) and Ulcerative Colitis (UC) may be complicated by the occurrence of strictures. They appear in 50% of patients after 20 years of CD evolution, but are less common in UC. The management of stricturing inflammatory bowel diseases has long been based on surgery and steroid therapy. In recent years and due to the advent of biologics, medical therapy has been increasingly used. Based on their clinical experience, physicians should be able to determine stricture features and patient characteristics to make the best tailored therapeutic decision. Anti-tumor necrosis factor (TNF) antibodies are currently the most effective drugs available in specific cases of stricturing CD.

Keywords Fibrostenoting IBD · Anti-TNF · Infliximab · Adalimumab · Prevention · Cancer · Crohn's disease · Ulcerative colitis

Abbreviations

CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index Score
ECM	Extracellular Matrix
HBI	Harvey Bradshaw Index
IBD	Inflammatory Bowel Diseases
OR	Odds Ratio
SES-CD	Simple Endoscopic Score in Crohn's Disease
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
UCEIS	Ulcerative colitis endoscopic index of severity

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15.1 Introduction

Inflammatory bowel diseases (IBD) are chronic relapsing disorders resulting in structural bowel damage over time. Both Crohn's disease (CD) and ulcerative colitis (UC) may be complicated by chronic inflammatory mechanisms triggering excessive extracellular matrix (ECM) production [1, 2]. The accumulation of collagen-rich ECM (fibrosis) in the intestinal wall leads to a narrowing of the gut lumen diameter and results in stenosis up to the point of occlusion [3]. Strictures are more common in CD, with an incidence of about 50% after 20 years of disease evolution [4]. Stricturing UC is less common, with a frequency ranging between 1.5% and 11.2% [5]. A prevalence of colonic strictures of 2.4% has been reported in IBD in a large retrospective study and colonic strictures appeared to be an independent risk factor for adenocarcinoma in the IBD population (OR = 8.42; $CI_{95\%}$ [3.85–16.79]) [6]. In this study, 80% of adenocarcinomas where located in the stricture site, a meticulous pathological assessment of the entire colonic mucosa is therefore essential, especially in stricturing IBD. The management of fibrostricturing IBD has for long been empirically based on surgery or endoscopy, and medical therapy was limited to steroids and bowel rest. Since the advent of biologics, the place of medical therapy has evolved in this clinical scenario.

15.2 Stricturing IBD: A Multifaceted Disease for Clinicians

15.2.1 Stricturing IBD

In clinical practice, the term "stricturing IBD" includes various diseases. There is no consensual definition for this condition and clinical study criteria, mainly used for the small bowel, vary from localized luminal narrowing to luminal narrowing and bowel wall thickening with pre-stricture dilation and the presence of obstructive symptoms [7–9]. A dilation of the upstream tract seems to be the most rigorous definition but it remains limited.

15.2.2 Stricturing CD

European guidelines define stricturing CD as a localized, persistent narrowing, whose functional effects may be apparent from prestenotic dilation, and include obstructive symptoms (EL5) [10]. In the Montreal classification, the B2 phenotype corresponds to intestinal strictures. It is important to keep in mind that the B3 phenotype corresponding to fistulizing intestinal disease is associated with intestinal strictures in more than 80% of cases so that stricturing CD is the most common complication of CD [11, 12]. Ileal stricture is the most common location due to

possibly due to location of inflammation and its narrow luminal diameter; 20% of fibrostenotic CD only affect the colon, and about 10% affect the upper tract [13, 14]. The prevalence of multifocal small bowel strictures has been estimated at 28.8% in a multicentric prospective cohort study conducted in B2 patients [15].

Stricturing CD may be diagnosed during an *endoscopic* procedure and is defined by a luminal narrowing, impossible or difficult to pass with an adult endoscope assessed using the CDEIS [16]. The SES-CD describes 3 groups of stricturing lesions with increasing significance: single passable narrowing (grade 1), multiple passable narrowing (grade 2) or impossible to pass (grade 3) [17]. Ileo-colonoscopy is recommended for the detection of colonic or ileal strictures.

Cross-sectional imaging (Magnetic resonance enterography (MRE) or CT enterography) is required in all cases of passable or non-passable strictures to assess their features and associated lesions. One study has suggested the superiority of enteroclysis in the diagnosis of low-grade stenosis [18]. The Lemann Index [19] allows defining stricturing lesions into three groups as a wall thickening <3 mm or segmental enhancement without prestenotic dilation (grade 1) or a wall thickening ≥3 mm or mural stratification without prestenotic dilation (grade 2) or a stricture with prestenotic dilation (grade 3). MRE is helpful to use another usual classification based on the discrimination between inflammatory, fibrotic or mixed narrowing (cf. Chap. 14) [20]. Predominantly inflammatory strictures are more likely to resolve through the use of anti-inflammatory drugs via edema resorption [21] but the distinction between inflammatory and fibrotic strictures, based on imaging criteria, is more theoretical than reflecting reality. A pathological study has shown that CD patients who undergo surgery for obstructive symptoms have mixed histopathological findings of inflammation, fibrosis and muscle hypertrophy [22]. It has also been shown and confirmed that inflammation was positively correlated with fibrosis in stenotic CD [23, 24].

Another definition of stricturing CD is a *capsule endoscopic retention* event. That is why in patients with small bowel CD capsule examination should be preceded by patency capsule [25]. The definition of retention is the capsule staying in the small bowel for longer than 2 weeks after ingestion, which may require endoscopic or surgical removal. It has been reported to occur from 0 to 13% of all examinations [26, 27]. Thus, patency capsule is required in patient with suspected intestinal stricture. If there is no impediment of patency progression, patency capsule should have passed out of the body within 30 h or observed in the colon on a radiograph or CT scan at least 30 h after being swallowed. All other cases are not considered patent and capsule endoscopy is contraindicated. Patency capsule retention is not specific for stricturing IBD, many other disease can cause retention such as tumors, larges polyps, radiation therapy, long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) [28]. In a CD population, capsule endoscopy retention occurs in 13%, while it occurs in 1.6% in a suspected CD population [27]. The sensitivity of patency capsule for detecting significant small bowel stricture is superior to other examinations [29, 30]. Positive predictive value of the patency capsule examination for detection of severe intestinal strictures vary from 44 to 62% [31, 32].

Clinically, symptoms of stricturing CD may range from highly symptomatic (Konïg syndrome caused by incomplete obstruction of small bowel, includes abdominal pain related to meal, constipation alternating with diarrhea, meteorism, gurgling sounds (hyper-peristalsis) on auscultation (especially in the right iliac fossa), and abdominal distension [33] to mildly symptomatic or asymptomatic. In case of asymptomatic strictures, it is essential to ensure that patients are on a normal diet, due to adaption of their diet based on stricture symptoms. In our practice, it is uncommon since patients usually are on a low-fiber diet, except in case of long-lasting strictures. Patients that adapt nutritional habits such as a low-residue or low-fiber diet, become secondarily asymptomatic. Because of its larger bowel diameter, a colonic stricture may remain asymptomatic, whereas a duodenal or ileal stricture may early be sub occlusive.

It is of note that there is a poor correlation between stricture symptoms and severity. Indeed, in a retrospective study including patients with long colonic CD strictures (6-cm length, $Q_{25–75\%}$ [4–10 cm]) who underwent surgery, 27% of patients were asymptomatic [34]. The clinical scores commonly used in CD based on stool frequency such as the Crohn's disease activity index (CDAI) [35] or Harvey Bradshaw Index (HBI) [36] are not adapted to monitor patients with stricturing CD. A small bowel narrowing may lead to sub occlusion with reduced stool number while a colonic stricture may lead to chronic diarrhea in addition to the inflammatory activity of the disease. There is no validated score to monitor symptomatic stricturing disease. The use of a specific score referred to as CDOS (Crohn's Disease Obstructive Score) based on symptoms related to bowel strictures (obstructive pain, nausea, vomiting, dietary restriction and occlusion) developed empirically in the CREOLE cohort study [15] has been suggested, but this score has not yet been validated.

Finally, before considering medical therapy in stricturing CD, stricture location, diameter, length (±5 cm [37]) and shape (a major angulation make endoscopic dilatation difficult or impossible) should be investigated. Other factors should be considered, including a distinct pathogenesis of anastomotic strictures that may be explained by a locally reduced vascular flow, high luminal pressure and bacterial stasis [38]. These parameters may impact the efficacy of medical therapy. Abscess and fistula may be more likely to occur in areas with high pressure, upstream of a stricture. The positive value of fistula to predict stricture has previously been shown to be 86.2% [39].

15.2.3 Stricturing UC

Stricturing UC should be separately considered, because of the high rate of dysplasia- or cancer-related stenosis. Patients with stricturing UC have a longer disease duration than those with non-stricturing UC [40]. ECCO guidelines recommend to perform a careful pathological assessment, complete colonoscopy or if impossible CT or MRI colonography [41].

The definition of stricturing UC has not been clearly characterized. A fixed narrowing of the colonic lumen excluding an obvious polypoid lesion is the most accepted definition in the literature. Both the UCEIS and endoscopic Mayo score do not allow grading strictures as a severity indicator [42, 43]. In most cases, colonic stricture is pauci- or asymptomatic. Symptomatic strictures are more likely to be malignant according to former studies based on mixed stricture definitions (colonoscopy or Barium Enema) [28, 29].

The prevalence of strictures in UC is underestimated and only old data are available. It varies from 0.4% [44] to 11.2% [45] depending on the definition. A large retrospective study including 1156 consecutive UC patients has shown that 59 (5%) patients had a stricturing disease and 9 (0.7%) patients had multiple strictures [5]. Among the 70 strictures, 17 (24%) were malignant. Three features were found to be associated with the presence of a malignant stricture: disease duration >20 years (61% risk of malignancy *versus* 0% if the disease duration was <10 years), location proximal to the splenic flexure (86% risk of malignancy *versus* 47 and 10% in the sigmoid and rectum) and obstructive symptoms. Among all strictures reported in the literature, 70–100% appear to be benign [5, 30, 31]. The rectal location seems to be the most common, and proximal strictures appear to be more often malignant.

It should be mentioned that there is an increased risk of dysplasia or cancer in case of colonic stricturing IBD. In a large retrospective study, an incidence of dysplasia or cancer in IBD colonic strictures (after surgery and dysplasia-free preoperative biopsies) of 3.5% has been reported (2.4% for CD and 10% for UC) [34].

15.3 Towards a Tailored Strategy

In IBD, one of the major challenges is to identify predictors for medical or non-medical therapy failure. To clearly determine the place of medical therapy in stricturing CD, it is important to define the clinical situations that can obviously not be medically treated: complete occlusion despite IV steroid course, bowel rest, IV fluids, and nasogastric tube require intestinal resection. A prestenotic dilation or local complications (abscess, fistula or peritonitis) are also usual surgical indications. A recent retrospective study including 221 subjects aimed to identify factors that predicted surgery within 2 years of hospitalization for CD, to guide medical versus surgical management decisions[46]. Multivariate modeling demonstrated small bowel dilation >35 mm (hazard ratio, 2.92; 95% confidence interval, 1.73–4.94) and a platelet: albumin ratio ≥ 125 (hazard ratio, 2.13; 95% confidence interval, 1.15–3.95) to predict surgery. The complications of surgical resection mainly include postoperative morbidity, the risk of transient stoma up to one third of patients and the high rate of postoperative surgical recurrence (44% at 10 years) [47]. Both British, American and European guidelines recommend endoscopic dilation (ED) in case of short (≤4 cm) symptomatic strictures, but surgery in case of longer strictures in addition to optimal medical systemic therapy [10, 12, 48, 49].

Table 15.1 Parameters to be considered for stricturing IBD management

Type of stricturing IBD	Strictures that should be considered for medical therapy	Strictures that should be considered for surgical therapy
Stricturing Crohn's disease	*Clinical features and patient characteristics* – Previous resection/short bowel syndrome – Current smoking – Naive to anti-TNF – Severe nutritional impairment – Short history of obstructive symptoms *Morphological features* – Multifocal strictures – Very long stricture (>40 cm) – Presence of inflammation (late contrast enhancement) – Limited dilation of the upstream tract (≤35 mm) – Absence of complex fistula *Histological features* Absence of dysplasia or adenocarcinoma	*Clinical features and patient characteristics* – No risk of short bowel syndrome – Previous failure of anti-TNF – Long history of obstructive symptoms – Low risk of postoperative recurrence *Morphological features* – Single stricture – Limited stricture (<40 cm) – Predominant fibrotic stricture – Large dilation of the upstream tract (>35 mm) – Presence of complex fistula, abscess *Histological features* Presence of dysplasia or adenocarcinoma
Stricturing ulcerative colitis	*Clinical features and patient characteristics* – Asymptomatic – Disease duration <20 years – Naive to anti-TNF *Morphological features* – Complete colonoscopy with careful biopsies throughout the colon – Single lesion – Absence of polypoid lesion – Rectal or sigmoid stricture *Histological features* – Absence of dysplasia or cancer	*Clinical features and patient characteristics* – Disease duration >20 years – Symptomatic – Previous failure of anti-TNF *Morphological features* – Proximal (before splenic flexure) – Non-passable, incomplete colonoscopy – Multifocal lesion *Histological features* – Presence of dysplasia or cancer

In other cases, the decision may be more difficult and clinicians need to be aware of the specific context. Previous resection, current smoking and penetrating disease are independent risk factors for postoperative recurrence, and should lead to initiation of medical therapy. A recent prospective cohort has shown that administering an anti-TNF therapy during the last 6 months before ileocecal resection increased the risk of postoperative morbidity [50]. These data stress the importance of implementing a tailored strategy (Table 15.1).

15.4 Medical Therapy in Fibrostricturing IBD

No specific anti-fibrotic drugs are currently available for treating the digestive tract [2]. Clinical trials assessing the efficacy of medical therapy on fibrosis-related UC strictures are lacking. Most publications are focused on CD.

15.4.1 Steroids

The effects of corticosteroids on fibrosis are unclear. Indeed, in in vitro studies, they have been shown to induce procollagen expression in human intestinal myofibroblasts [51]. On the other hand, a decreased procollagen expression has been reported with dexamethasone administration in animal models [45]. The indications of systemic steroid therapy are limited to brief (60 mg/day methylprednisolone for 5–7 days) IV bolus in symptomatic inflammatory strictures as a "therapeutic test" to induce clinical remission [52]. A former study has provided data on steroid infusions during occlusion due to small bowel strictures in 26 CD patients. Occlusion resolved within 72 h in 96% of cases, but 75% of patients experienced re-occlusion [53]. Corticosteroids have been shown to be an independent risk factor for postoperative morbidity as well as severe nutritional impairment and perforation [54, 55]. Using corticosteroids has been shown to be associated with intestinal stricture, or obstructive symptoms in the TREAT registry, as well as an ileal location and disease duration [56]. The long-term use of steroids should be avoided due to serious adverse events, and their known inability to induce mucosal healing, a condition necessary to prevent evolution to a fibrostricturing phenotype [57]. Intralesional injections of steroids did not seem to have a major impact on endoscopic dilation outcomes despite promising results in small case reports [58].

15.4.2 5-ASA

There is no evidence to support the use of 5-aminosalycilates (mesalamine) as a therapeutic agent or in the prevention of transmural stricturing CD [10]. Overall, in a meta-analysis, Hanauer and Strömberg have shown in CD that mesalamine may slightly reduce the CDAI with no clinical significance [59].

15.4.3 Purine Analogs

A prospective randomized study including 72 sub occlusive patients with ileal CD stricture, responding to IV steroids has compared the efficacy of mesalamine *versus* azathioprine 2–3 mg/kg [60]. The rate of rehospitalization-free survival was significantly higher in the azathioprine groups than in the mesalamine group, especially at 1 year. Among the 36 patients with azathioprine, the mean time to rehospitalization was 27 ± 10.4 months (*vs.* 18 ± 10.7 with mesalamine), 38.9% were admitted for occlusion and 22.2% for intestinal resection. There are not enough data available to support the use of purine analogs alone in stricturing CD.

Using azathioprine or 6-mercaptopurine has been shown to induce complete or partial mucosal healing of inflammatory ileitis following resection [61] and to delay clinical and endoscopic fibrostricturing recurrence after surgery [62]. Unexpectedly, the early prescription of thiopurines in naive patients did not change the rate of stricture occurrence or the frequency of surgical interventions [63]. More recently,

the POCER study has provided information about the post-operative medical strategy to be used to prevent CD recurrence. In the population with a high risk of recurrence (i.e. current smokers, previous resection and penetrating disease), purine analogs were prescribed in addition to metronidazole in the first 3 months after resection, and in case of intolerance, adalimumab was initiated. After 6 months, the most advanced forms of the disease (i3, i4 including stricture) were found in 8% of patients in the thiopurine group *vs.* 4% in the adalimumab group. Purine analogs did not appear to be the best medical therapy to prevent fibrostenoting CD.

15.4.4 Methotrexate

There is no specific data on the efficacy of methotrexate in fibrostricturing CD used either as a therapeutic or preventive agent. What is known is that mucosal healing is less frequently achieved with methotrexate than with thiopurines or infliximab in CD [64].

15.4.5 Anti-TNFs

The last two decades have seen the advent of anti-TNFs in severe IBD. Does stricturing CD benefit from anti-TNF therapy? In the early twenty-first century, retrospective studies have reported a potentially increased risk of complete bowel obstruction when using infliximab in stricturing CD [65, 66]. In 2006, Lichtenstein et al. have reported that the use of infliximab was not associated with stricture occurrence [67]. Between 2003 and 2011, three uncontrolled studies have confirmed the finding that using anti-TNFα (infliximab, n = 3) is safe and effective in inflammatory stricturing CD. Most of these studies included small bowel strictures, and stricture definition was heterogeneous [7, 54, 56]. A randomized controlled trial has stressed the preventive effect of infliximab intravenous injection for anastomotic stricture relapse (0% *vs.* 30% for Rutgeerts i4 at 1 year) [68].

The CREOLE study, a large prospective interventional cohort study, has recently provided more information about the safety and efficacy of adalimumab in CD patients with symptomatic small bowel stricture [15]. Stricture was defined as a constant luminal narrowing associated with upstream dilation or obstructive symptoms. They were defined using a score specifically built for this trial, the CDOS, to show that all patients had a severe clinical obstruction. After week 24, the treatment was successful in 62/97 (64%) patients. Thirty-five patients failed to achieve success for the following reasons: 14 needed corticosteroids after week 8, two patients were switched to infliximab, 8 patients underwent an intestinal resection, 2 patients had an endoscopic dilation, 10 patients had a severe adverse effect leading to adalimumab discontinuation, 2 patients interrupted adalimumab treatment and 5 patients withdrew from the study (four were lost to follow-up, one withdrew consent). In 8 cases, the failure was due to multiple reasons. After a long follow-up (3.8 ± 0.1 years), 29% of patients were still under adalimumab with no need for surgery or endoscopic dilation. Among patients in whom treatment was successful at week 24, 21

underwent subsequent intestinal resection and 64.9 ± 6.6% of patients did not need surgery 4 years after inclusion. The predictive factors for treatment success were analyzed using a multivariate analysis showing that the use of immunosuppressive agents at the time of adalimumab initiation, the presence of obstructive symptoms for <5 weeks and a CDOS >4, a small bowel stricture length <12 cm, a maximum small bowel diameter proximal to stricture(s) of 18–29 mm, a marked improvement in the delayed phase and the absence of fistula had an independent predictive value for adalimumab success (Table 15.2). In other words, combotherapy (immunosuppressant + adalimumab) seems to be more effective on short, symptomatic, inflammatory strictures with a short period of evolution. The median time to intestinal resection in the whole cohort was 3.8 years (Fig. 15.1). Because of the need to better

Table 15.2 Prognostic factors associated with a high success rate according to the CREOLE study

Factor/group with a high success rate	Coefficient estimate ± SE	Odds ratio estimate	p	Number of points
Immunosuppressant/yes	1.23 ± 0.62	3.42	0.040	1
CDOS/>4[a]	1.25 ± 0.65	3.48	0.046	1
Duration of obstructive symptoms (week)/<5	1.79 ± 0.81	6.00	0.016	1
Length of stricture (cm)/<12	1.80 ± 0.67	6.04	0.0042	1
Maximum proximal diameter (mm)/[18–29]	1.99 ± 0.68	7.32	0.0013	1
T1 delayed enhancement intensity/severe	1.78 ± 0.66	5.92	0.0034	1
Fistula/no	1.55 ± 0.76	4.72	0.035	1

[a]CDOS >4 is defined by daily mild to moderate obstructive pain with more than 3 days of associated nausea-vomiting, or severe obstructive pain during 1–7 days for the previous 8 weeks

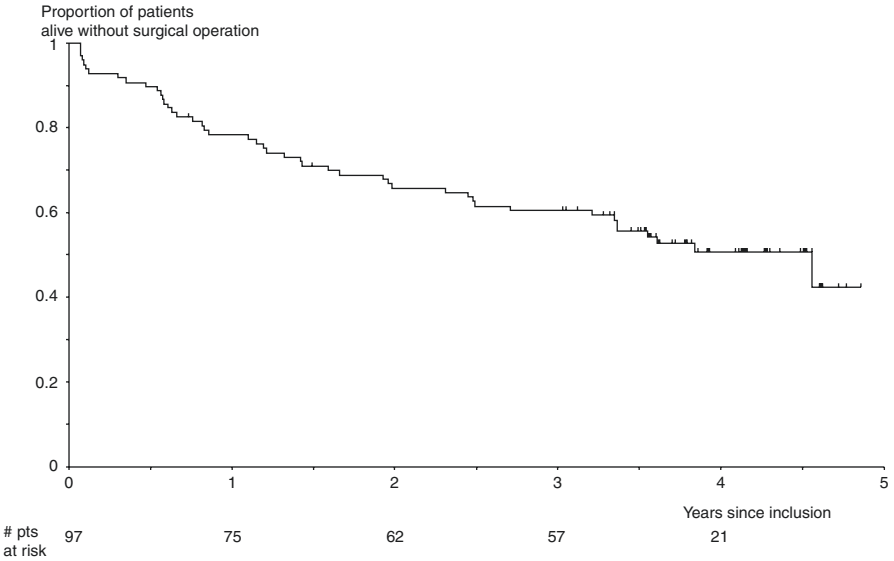

Fig. 15.1 Time to intestinal resection from inclusion in the 97 Crohn's disease patients with symptomatic small bowel stricture treated with anti-TNF (median follow-up ± SE, 3.8 ± 0.1 years, 46 resections were needed) [15]

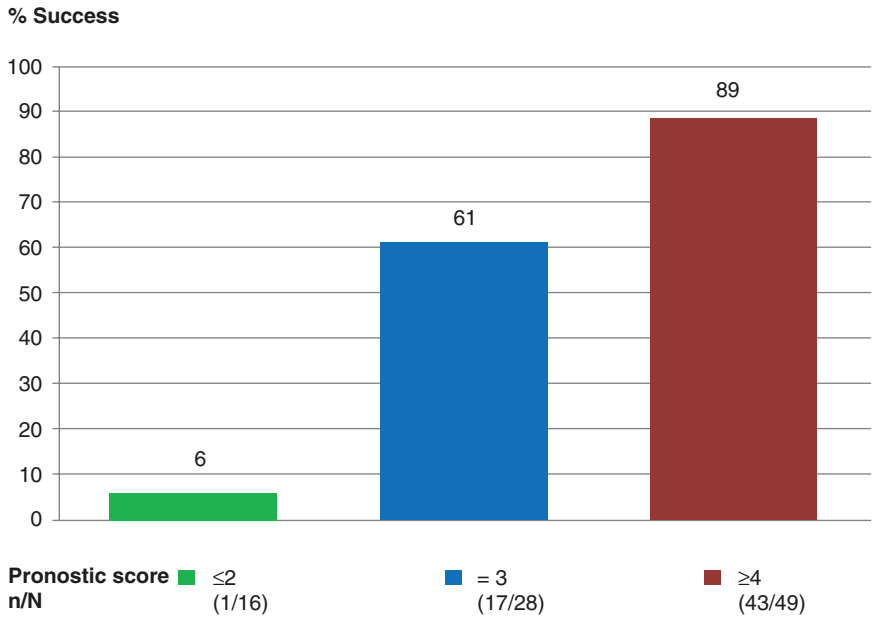

Fig. 15.2 Probability of success at week 24 in the 93 Crohn's disease patients withsymptomatic small bowel stricture(s) according to the clinicoradiological prognostic score [15]

determine in which patients' medical therapy will be successful, the authors have developed a prognostic score based on these parameters. Patients with a score of less than 3 points had a treatment success rate of 6% and in those with a score of at least 4 points, the treatment success rate was of 89% (Fig. 15.2).

15.4.6 Other Biologics

There are no specific data on the use of ustekinumab in stricturing CD. Symptomatic stricturing CD has been excluded from the UNITI studies [69]. The VICTORY consortium assessing vedolizumab use in a real-life setting in a CD population, included 118/212 (55.7%) patients with stricturing or penetrating CD, and after 12 months, resection was needed in 3 colonic and 2 small bowel strictures [70]. Mongersen (SMAD 7 antisense oligonucleotides) may restore TGFβ1 activity, leading to the inhibition of inflammatory pathways, and the resolution of enteritis in CD patients. TGFβ1 has also been shown to have profibrotic properties through stromal cell collagen stimulation [71]. In a phase I study, patients were closely monitored for the development of small bowel strictures by imaging and quantification of a fibrosis serological marker and no significant change was observed [72]. More data are

needed on the safety and efficacy of mongersen in stricturing IBD. However, phase 3 trials evaluating this drug in active CD patients were prematurely interrupted for lack of efficacy. No specific data are currently available on other biologics, such as janus kinase inhibitors, and fibrostricturing CD.

15.5 Other Measures

As in all chronic diseases, the medical treatment of stricturing IBD is not limited to pharmacological treatments. Medical therapy should always be based on a multimodal approach. ECCO guidelines recommend to treat patients with obstructive symptoms in the context of a multidisciplinary team (EL5) [73]. IBD are nutritional debilitating diseases and the intestinal narrowing worsens the nutritional impairment by increasing painful symptoms related to the alimentary bolus passage. In 2014, the British Dietetic Association has established guidelines for stricturing CD [74]. Oral or enteral nutritional supplementation may be required, especially in case of weight loss. Nutritional components that may cause a mechanical obstruction [e.g. fibrous parts of fruits and vegetables (skins, seeds, woody stalks), whole grains, nuts and seeds, gristle on meat, skin on meat or fish, edible fish bones] or food leading to excess gas production driving prestricturing pain should be excluded from the diet. Pre- or probiotics have been assessed in several studies but no obvious efficacy in maintaining remission or preventing or relieving stricturing IBD has been shown [66, 67, 75–77]. Current smoking worsens the clinical course and induces stricture occurrence in CD, reduces the therapeutic response, and is associated with post-surgical recurrence [78]. ECCO guidelines state that smoking is a risk factor for postoperative recurrence after resection or stricturoplasty for fibrostricturing CD (EL4) [73]. Therefore, all smoking patients with CD should be referred to a smoking cessation program (EL1) [10].

15.6 Conclusion

Medical therapy for stricturing IBD has recently become available. Anti-TNFs are currently the best molecules to be used in this context. Their administration implies the use of strict selection criteria to identify the best candidates and to balance the benefit-risk ratio with surgery. Further studies are needed to define the potential effect of other biologics in stricturing IBD. A major challenge for the coming years will be to identify a specific intestinal anti-fibrotic agent like those that are already available in skin healing [79], interstitial renal fibrosis [80], and systemic sclerosis [81].

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