INFLAMMATORY BOWEL DISEASE

Inflammatory stricturing crohn's disease: Results of medical treatment

Sabbah Meriam*; Ben Farhat Fatma; Bellil Nawel; Bibani Norsaf; Ouakaa Asma; Trad Dorra; Elloumi Héla; Gargouri Dalila

Department of gastroenterology, Habib Thameur Hospital, Tunisia.

Corresponding Author: Sabbah Meriam

Department of gastroenterology, Habib Thameur Hospital, Tunisia.

Email: sabbah_meriam@yahoo.fr

Abstract

Background: The relapsing and remitting character of CD results in accumulating damage to the bowel wall. Stricture is the most common complication of CD. Treatment of stricturing CD depends on the inflammatory or fibrotic character of the stricture. However, therapeutic management of stricturing CD remains a complex situation as it has been shown that inflammatory and fibrosis are two overlapping entities.

Aims: To assess the short and long-term impacts of medical treatment in inflammatory stricturing CD and to identify predictors of therapeutic failure and lead to surgery.

Patients and methods: We performed a retrospective study over a period of 15 years (2001-2016) where we included all patients with CD receiving medical treatment for symptomatic inflammatory stricture. The inflammatory nature of stricture was mainly identified by cross-sectional imaging examinations showing signs of active inflammation. Therapeutic failure was defined as symptomatic stricture leading to hospitalization or endoscopic dilation or surgery. Short and long term medical therapy failure were defined by occurrence of cited above events within respectively 6 and 24 months after initiation of medical therapy.

Results: Fifty-one inflammatory strictures were collected in 43 CD patients who received medical treatment. Medical therapy was based on a full-dose of oral corticosteroids in 33 cases (65%) and anti-TNF agents in 14 cases (27%). Four patients (7%) were treated by 5-Aminosalicylic Acid (5-ASA). Azathioprine (AZA) was prescribed in combination with corticosteroids in 21 cases (63%) and in combination with anti-TNF (combotherapy) in 12 patients (85%). The short-term therapeutic failure rate was 22 % (n = 11) and the long-term therapeutic failure rate was 45% (n = 23). Nineteen patients (37%) have been operated on within an average of 11 months (7-18 months). In univariate analysis, active tobacco (p=0,024), C - Reactive Protein (CRP)>28 mg/L (p=0,034) and the presence of fistulas (p=0,005) were significantly associated with short-term therapeutic failure. Active tobacco (p=0,005), young age at diagnosis (A1 according to the Montreal classification) (p=0,014), history of multiple use of corticosteroid≥3 times (p=0,001), CRP>28 mg/L (p=0,002) and presence of fistulas (p<10⁻³) were significantly associated to long-term failure. Use of anti-TNF agents was a protective factor against long-term therapeutic failure and surgery requirement (p=0,045).

In multivariate analysis, only the presence of fistulas was associated with short-term medical therapy failure (p=0,014).Active tobacco (p=0,009), age at diagnosis (A1 according to the Montreal classification) (p=0,036) and presence of enteroenteric fistulas (p=0,001) were independent predictors of long-term medical therapeutic failure and surgery requirement.

Conclusion: Despite the identification of inflammatory nature of intestinal stricture, medical treatment fails in half of the cases and nearly 40% of patients are operated on after 2 years. This emphasizes the fact that the two entities, inflammation and fibrosis, cannot be dissociated. Identify predictors of therapeutic failure, independent from the inflammation/fibrose dichotomy, may allow us to select from the outset patients at high risk of surgery.

Introduction

Stricture is the most common complication of CD, occurring in approximately one third of all patients with this condition [1]. It can appear in any segment of the digestive tract with a preferential location for the terminal ileum and ileocolic anastomoses [2]. Strictures can be inflammatory or fibrotic. This pathogenic consideration remains, however, speculative since both inflammatory and fibrotic compounds frequently occurred in association [3].

While endoscopic or surgical treatment including intestinal resection and stricturoplasty can be offered in case of fibrous stenosis, the treatment of inflammatory stenosis is medical. The development of biotherapy has increased the therapeutic potential of Crohn's strictures, but the efficacy of anti-Tumor Necrosis Factor-α antibodies in structuring CD remains controversial [4].

The aims of this study was to assess the short and long-term impacts of medical treatment in inflammatory stricturing CD and to identify predictors of therapeutic failure and lead to surgery.

Patient and methods

A retrospective study over a period of 15 years (2001-2016) including all patients with CD receiving medical treatment for symptomatic inflammatory stricture was conducted. The inflammatory nature of stricture was mainly identified by cross-sectional imaging examinations showing signs of active inflammation. Therapeutic failure was defined as symptomatic stricture leading to hospitalization or endoscopic dilation or surgery. Short and long-term medical therapy failure was defined by occurrence of cited above events within respectively 6 and 24 months after initiation of medical therapy.

Definitions and followup

- The diagnosis of Crohn's disease was based on all clinical, biological, endoscopic, morphological and histological arguments.

- The diagnosis of symptomatic stricture was made if clinical signs of obstruction and a narrowing of the intestinal lumen by morphological examinations (endoscopic +/- radiological) were objectified.

- Endoscopic stricture was defined by a narrowed aspect of the digestive lumen that did not allow the passage of the endoscope.

- The inflammatory nature of the stenosis was mainly retained in front of signs of radiological activity objectified to sectional imaging (CT-scanner, MRI), represented by:

  ✓ An intense enhancement with thickening of the wall

  ✓ Hyper intensity of the bowel wall on T2

  ✓ Pericolic or perienteric hypervascularity

  ✓ The presence of associated inflammatory lymphadenopathy.

- In cases where sectional imagery was not available, the inflammatory character was retained in front of an active disease with a CDAI> 220 and a high CRP level > 8 mg / L.

- The medical treatment of short and long term symptomatic stenosis was based on:

- Corticosteroids: Systemic corticosteroid prescribed at a dose of 1 mg / kg / day.

- 5-ASA derivatives: With an attack, dose of 4 g / d and a maintenance dose of 2 g / d.

- Immunosuppressant (azathioprine (AZA), 6 Mercaptopurine (6MP)) prescribed at doses of 2.5 mg / kg / jet from 1 to 1.5 mg / kg / day respectively.

- Anti-TNF alpha: Infliximab (IFX) at the starting dose of 5 mg / Kg at S0, S2 and S6 then every two months in maintenance in the event of a good response or adalinumab (ADA) at the dose of 160 mg at S0, 80 mg at S2 then 40 mg in maintenance every two weeks in the event of a good response.

- Parenteral nutrition (NP) in the event of severe undernutrition defined by a BMI <16 Kg / m^2 and / or albuminemia <30 g / L.

Statistical analysis

Quantitative variables were presented as the median and percentile (I. Q. R. for interquartile range: 25% and 75%).Regarding follow-up, the data was censored when the failure was defined or when the last news was reported. The differences between continuous and categorical variables were examined for statistical significance using the Student's t test (or the Mann-Whitney test, if applicable) and the chi-square test (or the exact test of Fisher, if applicable). The data concerning the effectiveness of medical treatment in terms of time to clinical recurrence and time to resort to surgery were analyzed by survival curves according to the Kaplan-Meier method. Continuous variables were dichotomized at a significant threshold established using the ROC curve, if this did not exist, these variables were dichotomized at the median. The Log Rank test was used to compare the survival curves and assess the predictive significance of the variables tested. To estimate the predictors of medical treatment failure, multivariate and univariate Cox proportional risk regression analyzes were performed. The corresponding 95% risk ratios (HR) and confidence intervals (CI) were used where indicated.

For all statistical analyzes, the significance level was set at 0.05.

Results

Study population

Fifty-one inflammatory strictures were collected in 43 CD patients who received medical treatment. The baseline characteristics of these 43 patients are listed in Table 1.

Table 1: Baseline characteristics of the studied population

(%) or median [IQR 25–75]	N=43
Sex (M/F)	1,21 (24/19)
Smoking	21
Age at CD diagnosis (years)	32 [16,74]
Montreal classification at CD diagnosis	
A1 < 16	8
A2 < 40	22
A3 ≥ 40	13
L1-ileal	26
L2-colonic	2
L3-ileocolonic	23
L4- upper digestive tract	3
B1-nonpenetratingnonstricturing	20
B2- structuring	17
B3- penetrating	14
Extra-intestinal manifestations	
Number of Outbreaks	7
1	8
2	6
3	12
Prior treatments Surgery	
Ileal resection	4
Ileal and colonic resection	19
colonic resection	2
Medical treatment	
5 ASA	7
Immunosuppressant (AZA or MTX or 6MP)	12
No treatment	24

Stricture characteristics

In patients with no history of previous resection (n = 24), the Crohn Disease Activity Index (CDAI) was calculated. Active disease was noted in 19 patients. Two patients had mild activity (CDAI between 150 and 220), 15 patients had moderate activity (CDAI between 220 and 450) and two patients had severe CD (CDAI> 450).

Five patients had a severe denutrition (BMI<16 kg/m^2).

The CRP was greater than 8 mg / d in 35 cases (68%) and more particularly greater than 25 mg /dL in 26 cases (50.9%).

Table 2: Characteristics of the strictures according to sectional imaging data

	CT scan n=33/ MRI n=6
Multiple	14(30%)
Unique	32(70%)
Type Non anastomotic Anastomotic	33(67%) 25(51%)
Localization of non-anastomotic stricture (n=40) Duodenum Proximal ileum Terminal ileum Right colon Transverse colon Left colon Rectum	1(3%) 5(12%) 27(67%) 1(3%) 1(3%) 3(7%) 2(5%)
Localization of anastomotic stricture (n=24) GEA Ileo-colic Ileo-ileal	1(4%) 21(84%) 2(8%)
Length (cm)	10,5 (3-20)
Inflammatory lesion activity Degree of enhancement Intense Moderate Absent Hyperintensity of the bowel wall on t2 Intense Moderate Absent Pericolic or perienterichypervascularity (comb sign) Mesenteric lymphadenopathy Prestenotic dilatation Absent Moderate Important	30(90%) 3(10%) 0 6(100%) 0 0 30(76%) 36(92%) 18(46%) 18(46%) 2(5%)
Luminaldiameter (mm)	3,2(2,4-4,2)
Degree of wall thickening (mm)	11,9(11-14)
Enteroenteric fistulas	19(48%)

Medical Treatment

Medical therapy was based on a full-dose of oral corticosteroids in 33 cases (65%) and anti-TNF agents in 14 cases (27%).

Four patients (7%) were treated by 5-aminosalicylic acid (5-ASA). Azathioprine (AZA) was prescribed in combination with corticosteroids in 21 cases (63%) and in combination with anti-TNF (combotherapy) in 12 patients (85%).

The short-term therapeutic failure rate was 22 % (n = 11) and the long-term therapeutic failure rate was 45% (n = 23).

Nineteen patients (37%) have been operated on within an average of 11 months (7-18 months). In univariate analysis, active tobacco (p=0,024), C-Reactive Protein (CRP)>28 mg/L (p=0,034) and the presence of fistulas (p=0,005) were significantly associated with short-term therapeutic failure. Active tobacco (p=0,005), young age at diagnosis (A1 according to the Montreal classification) (p=0,014), history of multiple use of corticosteroid ≥3 times (p=0,001), CRP>28 mg/L (p=0,002)

and presence of fistulas (p<10^{-3}) were significantly associated to long-term failure. Use of anti-TNF agents was a protective factor against long-term therapeutic failure and surgery requirement (p=0,045).

In multivariate analysis, only the presence of fistulas was associated with short-term medical therapy failure (p=0,014). Active tobacco (p=0,009), age at diagnosis (A1 according to the Montreal classification) (p=0,036) and presence of enteroenteric fistulas (p=0,001) were independent predictors of long-term medical therapeutic failure.

Discussion

In our study, although we only included inflammatory stricture, the percentage of successful medical treatment was estimated at 55%. This may be due to the fact that most of the digestive strictures during CD were mixed: both inflammatory and fibrous. It has become commonplace to categorize small intestinal Crohn's disease (CD) as "active" vs. "inactive" or "inflammatory" vs. "fibrotic" based on Computed Tomography Enterography (CTE) findings but Adler and al had shown that small bowel stricture without CTE findings of inflammation does not predict the presence of tissue fibrosis [5]. Another study of Zappa and al also showed that fibrosis was closely and positively related to inflammation [6].

Many studies showed that the outcomes of medical treatment of stricturing or penetrating CD are poor, as 64% ultimately require surgery [7,9].The only medical treatment evaluated during digestive stenosis of CD is represented by anti-TNF alpha [2]. In our series, the medical treatment of inflammatory stenosis included systemic corticosteroid therapy and anti-TNF.

Samimi, et al found that Corticosteroid therapy was effective in 41% of the patients on day 180 and 50% of the treated patients ended up being operated [7]. These results are comparable to those of our study.

Treatment of small bowel subocclusive Crohn's disease with infliximab is controversial. In fact, according to some studies the anti-TNF drugs could increase the risk of stenosis, due to the accelerated healing process leading to a marked architectural change in the intestinal wall with scarring and potential fibrosis [10,12]. However, promising results regarding the use of infliximab have been reported in other studies: 94.4% had clinical improvement after the IFX induction phase and 44% of complete remission [13,14].

In our study, factors associated with short-term therapeutic failure were active tobacco, C-Reactive Protein (CRP)>28 mg/L, and the presence of fistulas in univariate analysis and those associated with long-term therapeutic failure are Active tobacco, young age at diagnosis (A1 according to the Montreal classification), history of multiple use of corticosteroid ≥3 times, CRP>28 mg/L and presence of fistulas.

This association was found in other studies [15-24]. Other factors have been reported: The duration of the disease and ileal location of the stricture [25-27].

However, the anastomotic stricture is not associated with therapeutic failure but is a predictive factor for resorting to surgery [28]. The length of the stricture is not a factor influencing treatment failure [29,30]. A moderate pre-stenotic dilation with maximum diameter of the small intestine upstream of the stenosis between 18 and 29 mm was a predictive factor for the success of ADA treatment [31].

Table 3: Factors associated with therapeutic failure in the litterature

Factors associated with short-term therapeutic failure	Factors associated with long-term therapeutic failure
• active tobacco • C-reactive protein (CRP)>28 mg/L • the presence of fistulas • the duration of the disease • ileal location of the stricture • CDAI < 220 • Prestenotic dilatation >3cm	• Active tobacco • young age at diagnosis (A1 according to the Montreal classification) • history of multiple use of corticosteroid ≥3 times • CRP>28 mg/L and presence of fistulas. • Obstructive symptoms

In view of our results and by reviewing the literature, we can propose an algorithm for the management of inflammatory stenosis during Crohn disease (Figure 1).
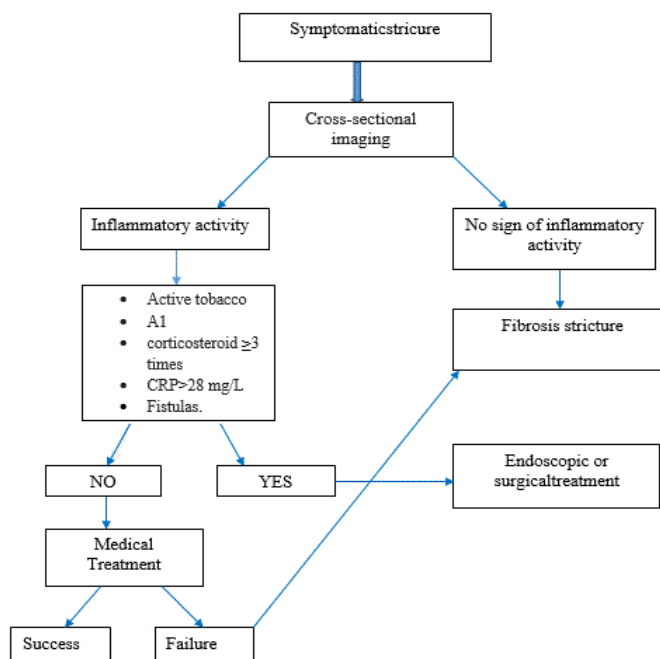

Figure 1: Management of inflammatory stenosis during Crohn disease

Conclusion

Despite the identification of inflammatory nature of intestinal stricture, medical treatment fails in half of the cases and nearly 40% of patients are operated on after 2 years. This emphasizes the fact that the two entities, inflammation and fibrosis, cannot be dissociated. Identify predictors of therapeutic failure, independent from the inflammation/fibrose dichotomy, may allow us to select from the outset patients at high risk of surgery.

References

1. Vrabie R, Irwin GL, Friedel D. Endoscopic management of inflammatory bowel disease strictures. World J GastrointestEndosc. 2012; 4: 500-505.

2. Rieder F, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: A systematic review. Gut. 2013; 62: 1072-1084.

3. Brochard C, Siproudhis L, Wallenhorst T, Cuen D, d'Halluin PN, et al. Anorectal stricture in 102 patients with Crohn's disease: Natural history in the era of biologics. Aliment PharmacolTher. 2014; 40: 796-803.

4. Condino G, Calabrese E, Zorzi F, Onali S, Lolli E, et al. Anti-TNF-alpha treatments and obstructive symptoms in Crohn's disease:

A prospective study. Dig Liver Dis. 2013; 45: 258-262.

5. Adler J, Punglia DR, Dillman JR, Polydorides AD, Dave M, et al. Computed tomography enterography findings correlate with tissue inflammation, not fibrosis in resected small bowel Crohn's disease. Inflamm Bowel Dis. 2012; 18: 849-856.

6. Zappa M, Stefanescu C, Cazals-Hatem D, Bretagnol F, Deschamps L, et al. Which magnetic resonance imaging findings accurately evaluate inflammation in small bowel Crohn's disease? A retrospective comparison with surgical pathologic analysis. Inflamm Bowel Dis. 2011; 17: 984-993.

7. Samimi R, Flasar MH, Kavic S, Tracy K, Cross RK. Outcome of medical treatment of stricturing and penetrating Crohn's disease: A retrospective study. Inflamm Bowel Dis. 2010; 16: 1187-1194.

8. PeyrinBiroulet L, Oussalah A, Williet N, Pillot C, Bresler L, et al. Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. Gut. 2011; 60: 930-936.

9. Cosnes J, NionLarmurier I, BeaugerieL, Afchain P, Tiret E, et al. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. Gut. 2005; 54: 237-241.

10. Louis E, Boverie J, Dewit O, Baert F, De Vos M, et al. Treatment of small bowel suboccluse Crohn's disease with infliximab: An open pilot study. Acta Gastro-Enterol Belg. 2007; 70: 15-19.

11. Vasilopoulos S, Kugathasan S, Saeian K, Emmons JE, Hogan WJ, et al. Intestinal strictures complicating initially successful infliximab treatment for luminal Crohn's disease. Am J Gastroenterol. 2000; 95: 2503.

12. Zorzi F, Zuzzi S, Onali S, Calabrese E, Condino G, et al. Efficacy and safety of infliximab and adalimumab in Crohn's disease: A single centre study. Aliment PharmacolTher. 2012; 35: 1397-1407.

13. Pelletier AL, Kalisazan B, Wienckiewicz J, Bouarioua N, Soulé JC. Infliximab treatment for symptomatic Crohn's disease strictures. Aliment PharmacolTher. 2009; 29: 279-285.

14. Pallotta N, Barberani F, Hassan NA, Guagnozzi D, Vincoli G, et al. Effect of infliximab on small bowel stenoses in patients with Crohn's disease. World J Gastroenterol. 2008; 14: 1885-1890.

15. Duricova D, Burisch J, Jess T, Gower-Rousseau C, Lakatos PL. Age-related differences in presentation and course of inflammatory bowel disease: An update on the population-based literature. J CrohnsColitis. 2014; 8: 1351-1361.

16. Lichtenstein GR, Olson A, Travers S, Diamond RH, Chen DM, et al. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. Am J Gastroenterol. 2006; 101: 1030-1038.

17. Rieder F, Lawrance IC, Leite A, Sans M. Predictors of fibrostenotic Crohn's disease. Inflamm Bowel Dis. 2011; 17: 2000-2007.

18. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: A meta-analysis. Mayo Clin Proc. 2006; 81: 1462-1471.

19. Kuenzig ME, Lee SM, Eksteen B, Seow CH, Barnabe C, et al. Smoking influences the need for surgery in patients with the inflammatory bowel diseases: A systematic review and meta-analysis incorporating disease duration. BMC Gastroenterol. 2016; 16: 143.

20. Cottone M, Rosselli M, Orlando A, Oliva L, Puleo A, et al. Smoking habits and recurrence in Crohn's disease. Gastroenterology. 1994; 106: 643-648.

21. Magro F, Rodrigues-Pinto E, Santos-Antunes J, Vilas-Boas F, Lopes S, et al. High C-reactive protein in Crohn's disease patients predicts nonresponse to infliximab treatment. J Crohns Colitis. 2014; 8: 129-136.

22. Henriksen M, Jahnsen J, Lygren I, Stray N, Sauar J, et al. C-reactive protein: A predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. Gut. 2008; 57: 1518-1523.

23. Campos C, Perrey A, Lambert C, Pereira B, Goutte M, et al. Medical Therapies for stricturing Crohn's Disease: Efficacy and cross-Sectional imaging predictors of therapeutic failure. Dig Dis Sci. juin 2017; 62: 1628-1636.

24. Bouhnik Y, Carbonnel F, Laharie D, Stefanescu C, Hébuterne X, et al. Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: A multicentre, prospective, observational cohort (CREOLE) study. Gut. 2018; 67: 53-60.

25. Golovics PA, Mandel MD, Lovasz BD, Lakatos PL. Inflammatory bowel disease course in Crohn's disease: Is the natural history changing?. World J Gastroenterol. 2014; 20: 3198-3207.

26. Louis E, Collard A, Oger AF, Degroote E, El Yafi FA, et al. Behaviour of Crohn's disease according to the Vienna classification: Changing pattern over the course of the disease. Gut. 2001; 49: 777-782.

27. Louis E, Michel V, Hugot JP, Reenaers C, Fontaine F, et al. Early development of stricturing or penetrating pattern in Crohn's disease is influenced by disease location, number of flares, and smoking but not by NOD2/CARD15 genotype. Gut. 2003; 52: 552-557.

28. Campos C, Perrey A, Lambert C, Pereira B, Goutte M, et al. Medical Therapies for Stricturing Crohn's Disease: Efficacy and Cross-Sectional Imaging Predictors of Therapeutic Failure. Dig Dis Sci. 2017; 62: 1628-1636.

29. Bossuyt P, Debeuckelaere C, Ferrante M, de Buck van Overstraeten A, Vanbeckevoort D, et al. Risk stratification for surgery in stricturing ileal Crohn's disease: The BACARDI risk model. Journal of Crohn's and Colitis. 2018; 12: 32-38.

30. Mao R, Chen BL, He Y, Cui Y, Zeng ZR, et al. Factors associated with progression to surgery in Crohn's disease patients with endoscopic stricture. Endoscopy. 2014; 46: 956-962.

31. Bouhnik Y, Carbonnel F, Laharie D, Stefanescu C, Hébuterne X, et al. Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: A multicentre, prospective, observational cohort (CREOLE) study. Gut. 2018; 67: 53-60.