

Treatment patterns and outcomes of patients with complex Crohn's perianal fistula in five European countries: the PREFACE study

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Abstract

Background and study aims: Crohn's disease (CD) is often complicated by perianal fistulas or abscesses that worsen patient's quality of life, with 52-88% of CD-related perianal fistulas (CPFs) being complex. This retrospective study describes socio-demographic characteristics, treatment patterns and outcomes of patients with complex CPFs in five European countries.

Patients and methods: PREFACE is a multi-national medical chart review study of CD patients who started medical or surgical treatment for a new episode of complex CPFs between September 2011 and September 2014 (index date). Effectiveness outcomes were assessed as fistula remission rates based on fistula drainage assessment. The most recent assessments prior to each timepoint were used to calculate fistula remission rates.

Results: In total, 372 patients (51.3% male, mean age at index date 37.8 years) with 498 complex CPFs between index date and end of data collection were included. A quarter of patients with CPF already had perianal fistulas at CD diagnosis.

Of the complex index CPFs, 39.8% were treated with anti-tumour necrosis factor, 33.3% with antibiotics and 16.3% with immunosuppressants. At least one surgery was performed for 93.8% of complex CPFs. By end of follow-up (median (IQR) 6.0 (5.2, 6.9) years), 61.2% of complex CPFs were not draining anymore. Fistula remission rate at patient level was 28.0% after 6 months, 35.2% after 12 months and 64.8% overall.

Conclusions: Current therapeutic algorithms for CPFs are not successful in a considerable proportion of patients. Improved therapeutic strategies and new treatment options are required to achieve better outcomes in complex CPFs. (*Acta gastroenterol. belg.*, 2024, 87, 494-504).

Keywords: Complex perianal fistula, Crohn's disease, anti-TNF, fistula remission.

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the digestive tract of unknown aetiology that appears to be triggered by the interaction of genetic and environmental factors. CD is a progressive disease with alternating periods of active inflammation and clinical remission, and long-term accumulation of damage if not properly controlled (1).

Patients with CD may suffer from abdominal pain, severe diarrhoea, fatigue, weight loss, and malnutrition, depending on the severity of the disease. CD may be complicated with the formation of ulcers, strictures, fistulas, and abscesses. It may affect people in early childhood until late adulthood and has a significant impact on patient's quality of life (1).

There is no definitive cure for CD. The aim of currently available therapies is to manage and avoid flares by inducing and maintaining clinical and endoscopic remission (1,2).

When the perianal area is affected, it is common for fistulas and abscesses to appear causing further deterioration in the patient's quality of life. In patients with CD the cumulative incidence of perianal fistula is estimated to be 26-28% over a period of 20 years (3). Appearance of fistulas and abscesses has also been considered an indicator of poor prognosis (4,5) and increased health care costs (6,7).

The American Gastroenterological Association proposed a simplified classification of perianal fistulas that provides a practical approach to assessing perianal lesions by dividing them into two categories: simple or complex. A simple fistula is low (superficial or low intersphincteric or low transsphincteric origin of the fistula tract), has a single external opening, and is not associated with 1) pain or fluctuation to suggest perianal abscess, 2) a rectovaginal fistula, or 3) an anorectal stricture. A complex fistula is high (high intersphincteric or high transsphincteric or extrasphincteric or suprasphincteric origin of the fistula tract), may have multiple external openings, may be associated with 1) the presence of pain or fluctuation to suggest a perianal abscess, 2) a rectovaginal fistula, 3) an anorectal stricture, or 4) active rectal disease at endoscopy. This division is made on the basis of fistula tract anatomy, number of external openings, presence of abscesses and/or proctitis (8,9). This classification has prognostic relevance for fistula remission as patients with more complex fistula are less likely to achieve fistula healing (no discharge mentioned during clinical history and no discharge shown during clinical examination) than patients with simple fistulas and have a high rate of fistula recurrence when therapy is discontinued (10). In epidemiological studies in CD

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Table 1. — Eligibility criteria

Inclusion Criteria
Documented diagnosis of CD with complex CPF (as per the American Gastroenterological Association definition ⁶).
Patient at least 18 years old at index date.
Treatment initiation (either first treatment after diagnosis or after fistula remission period of at least 6 months) for a new episode of complex CPF between Sept 2011 and Sept 2014.
Treatment mainly for perianal disease according to physician's criteria ⁷ .
Patient follow-up at the participant site for CD for at least 3 years after the index date, except if the cause of lost to follow up was death.
Provided informed consent (if required following local regulations).
Exclusion criteria
Participation in an interventional clinical trial during the 3-year follow-up period.
Diagnosis of inflammatory bowel disease type unclassified (IBDU).
Diagnosis of ulcerative colitis.
Abbreviations: CD = Crohn's disease; CPF = CD-related perianal fistulas. † Patients for luminal disease were not included in the analyses.

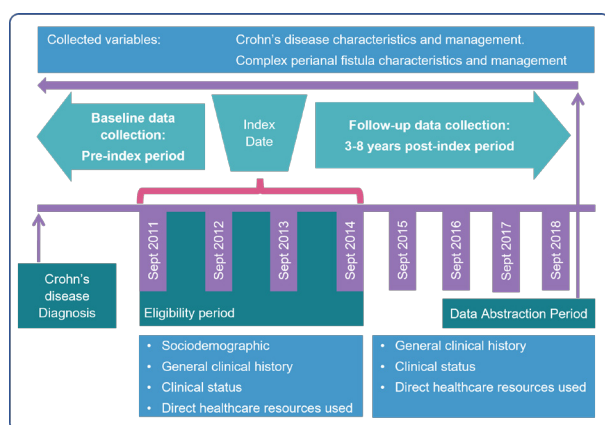


Figure 1. — Study design and study periods.

patients with fistulas, approximately 52-88% of CD-related perianal fistulas (CPFs) are complex (11).

The treatment goals in CPFs management are to resolve fistula discharge, achieve fistula healing, preserve faecal continence and avoid a proctectomy; all of this leading to improvement in patient's quality of life (12). Clinicians agree that corticosteroids and aminosalicylates are not recommended options (12). The use of antibiotics such as metronidazole and ciprofloxacin is recommended as adjunctive therapy only (so only in addition to another treatment); similarly immunosuppressants such as thiopurines, methotrexate, tacrolimus and cyclosporine may have a moderate effect on healing the complex CPFs (13,14). The European Crohn's and Colitis Organisation (ECCO) guidelines state that the first line treatment for complex CPFs should be biologic therapy with either infliximab or adalimumab (both anti-Tumour Necrosis Factor (TNF) antibodies), combined with surgery when required; combined therapy with ciprofloxacin and anti-TNF may also improve complex CPF outcomes for the short term (15).

The management of CPF also includes surgical measures, primarily fistula and abscess drainage and as

a next step primary or secondary fistula repair. Surgical repair of fistulas can comprise sphincter-preserving procedures including the conduct of a mucosal flap surgery, ligation of intersphincteric fistula tract (LIFT), endorectal pull-through or other methods like laser. Proctectomy with a permanent ostomy should be the last option for patients with severe disease who are refractory to other treatments (12).

There are few studies specifically designed to assess treatment outcomes in complex CPF. A recent literature review revealed that treatment success is highly variable even when using the newest drug therapies and surgical procedures, concluding that patients with complex CPFs still suffer unmet needs (12,16).

In our retrospective chart review study, we describe the demographic characteristics, treatment patterns and outcomes of patients with complex CPF receiving treatment for a new episode of complex CPF during the eligibility period in five European countries.

Materials and Methods

Study design

PREFACE is a retrospective multi-national, multi-centre medical chart review study including patients with CD who started medical or surgical treatment for a new episode of complex CPF between September 2011 and September 2014.

Data from medical charts and notes were retrieved for consecutive patients with CD receiving treatment for a new episode of complex CPF during the eligibility period in Belgium (6 sites), France (7 sites), Germany (3 sites), Italy (13 sites) and Spain (4 sites). Patients were identified according to the eligibility criteria (Table 1) starting September 2014 and going backwards until September 2011 (eligibility period) (Figure 1).

The index date was defined as the date of any medical or surgical treatment initiation for a new episode of

Table 2. — Tests or procedures performed by patients during the follow-up period

Tests or Procedures		Belgium (N=42)	Italy (N=216)	France (N=94)	Spain (N=7)	Germany (N=13)	Overall (N=372)
Complete blood cell count	Used	42 (100.0%)	216 (100.0%)	86 (91.5%)	7 (100.0%)	13 (100.0%)	364 (97.8%)
	Not used	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	8 (8.5%)	0 (0.0%)	0 (0.0%)	8 (2.2%)
Coagulation testing	Used	37 (88.1%)	207 (95.8%)	66 (70.2%)	4 (57.1%)	13 (100.0%)	327 (87.9%)
	Not used	5 (11.9%)	9 (4.2%)	20 (21.3%)	0 (0.0%)	0 (0.0%)	34 (9.1%)
	Missing	0 (0.0%)	0 (0.0%)	8 (8.5%)	3 (42.9%)	0 (0.0%)	11 (3.0%)
Electrolyte analysis/ renal function assessment	Used	42 (100.0%)	206 (95.4%)	73 (77.7%)	4 (57.1%)	13 (100.0%)	338 (90.9%)
	Not used	0 (0.0%)	10 (4.6%)	12 (12.8%)	1 (14.3%)	0 (0.0%)	23 (6.2%)
	Missing	0 (0.0%)	0 (0.0%)	9 (9.6%)	2 (28.6%)	0 (0.0%)	11 (3.0%)
Liver function test	Used	42 (100.0%)	199 (92.1%)	78 (83.0%)	4 (57.1%)	12 (92.3%)	335 (90.1%)
	Not used	0 (0.0%)	17 (7.9%)	8 (8.5%)	0 (0.0%)	1 (7.7%)	26 (7.0%)
	Missing	0 (0.0%)	0 (0.0%)	8 (8.5%)	3 (42.9%)	0 (0.0%)	11 (3.0%)
Stool studies	Used	28 (66.7%)	152 (70.4%)	74 (78.7%)	7 (100.0%)	5 (38.5%)	266 (71.5%)
	Not used	14 (33.3%)	64 (29.6%)	15 (16.0%)	0 (0.0%)	8 (61.5%)	101 (27.2%)
	Missing	0 (0.0%)	0 (0.0%)	5 (5.3%)	0 (0.0%)	0 (0.0%)	5 (1.3%)
X-ray	Used	30 (71.4%)	145 (67.1%)	56 (59.6%)	6 (85.7%)	1 (7.7%)	238 (64.0%)
	Not used	12 (28.6%)	71 (32.9%)	34 (36.2%)	1 (14.3%)	12 (92.3%)	130 (35.0%)
	Missing	0 (0.0%)	0 (0.0%)	4 (4.3%)	0 (0.0%)	0 (0.0%)	4 (1.1%)
Computed tomography	Used	26 (61.9%)	103 (47.7%)	55 (58.5%)	1 (14.3%)	3 (23.1%)	188 (50.5%)
	Not used	16 (38.1%)	113 (52.3%)	38 (40.4%)	6 (85.7%)	10 (76.9%)	183 (49.2%)
	Missing	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Magnetic resonance imaging scan	Used	39 (92.9%)	199 (92.1%)	90 (95.7%)	7 (100.0%)	6 (46.2%)	341 (91.7%)
	Not used	3 (7.1%)	17 (7.9%)	3 (3.2%)	0 (0.0%)	7 (53.9%)	30 (8.1%)
	Missing	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Total colonoscopy / ileocolonoscopy	Used	37 (88.1%)	193 (89.4%)	91 (96.8%)	7 (100.0%)	12 (92.3%)	340 (91.4%)
	Not used	(11.9%)	23 (10.7%)	2 (2.1%)	0 (0.0%)	1 (7.7%)	31 (8.3%)
	Missing	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Proctology	Used	18 (42.9%)	169 (78.2%)	77 (81.9%)	3 (42.9%)	12 (92.3%)	279 (75.0%)
	Not used	24 (57.1%)	47 (21.8%)	13 (13.8%)	4 (57.1%)	1 (7.7%)	89 (23.9%)
	Missing	0 (0.0%)	0 (0.0%)	4 (4.3%)	0 (0.0%)	0 (0.0%)	4 (1.1%)

complex CPF during the eligibility period, i.e. first episode or first symptom either after diagnosis or after a period of fistula remission of at least 6 months. The period between the diagnosis of CD and the index date was defined as the pre-index period and the period following the index date was defined as the post-index period (Figure 1).

The sample size was calculated based on statistical criteria. In order to estimate dichotomous variables with a probability of occurrence of 0.50 with a precision of 0.045 and a significance level of 0.05 a total sample of 475 patients at overall level was required corresponding to 95 patients per country. Due to a lack of eligible patients in some countries, 372 patients were included, resulting in a precision level of between 0.05 and 0.06 and maintaining a significance level of 0.05.

All patients who met the eligibility criteria were included in the study population. The following variables were abstracted from the patients' medical charts and

physician notes: socio-demographics, general clinical data, characteristics and management of CD and complex CPFs including clinical status of the complex CPFs, medications and surgical interventions for complex CPFs and health care resources used. Health care resource utilization is not further discussed in this manuscript.

Treatment outcomes

Treatment outcomes were analysed at fistula level and, additionally, at patient level for complex CPFs at index date.

At fistula level, treatment outcomes were assessed for each treatment prescribed based on fistula drainage assessment (20) and rated as either 'open' (actively draining), 'closed' (no external opening and no drainage despite gentle finger compression) or 'in fistula remission' (presence of external opening and absence of any draining fistulas despite gentle finger compression). 'Closed' and 'in fistula remission' were combined to

'in fistula remission' for outcome analysis. In addition, the tests or procedures performed during the follow-up period were assessed, with most patients (91.67%, n=341) reporting to have performed MRI at least once during the follow-up period (Table 2). All complex CPFs collected in the study from index date to date of data collection were included in the analysis. For each complex CPF overall effectiveness was reported at the end of the individual follow-up period. If more than one treatment (surgical and/or medical treatment) was applied, the last fistula drainage assessment reported in the case report form (CRF) and the corresponding date was used for analysis.

At patient level, outcome was analysed only for the complex CPF reported at index date. Fistula remission rates at 6 ($\pm$ 1) and 12 ($\pm$ 1) months after index date and at the end of the individual follow-up period were analysed. Patients not reaching the corresponding follow-up (i.e. 6 months) period were excluded from this analysis. Complex CPFs' status (open or in fistula remission) were analysed at each timepoint (i.e. 6 or 12 months) based on the last fistula drainage assessment with date available prior to the corresponding timepoint.

For all patients with complex index CPF in fistula remission at 6 ($\pm$ 1), 12 ($\pm$ 1) months and at the end of the individual follow-up period the number of re-interventions from index date until the corresponding timepoint was calculated. The following interventions were considered: a) prescription of a new treatment with anti-TNF or immunosuppressant at least 30 days after index date and prior to complex CPF remission date; b) surgery for complex CPF performed at least 30 days after index date and prior to complex CPF remission date; c) hospitalization categorized as 'possible related to relapse' at least 30 days after index date and prior to complex CPF remission date.

Statistical methods

Continuous variables were described with number of patients with valid/missing observations, mean, standard deviation (SD), median, and quartiles Q1 and Q3. Categorical variables were described with valid/missing observations, and number and percentage of responses per category.

Skewed continuous outcomes were compared using the Wilcoxon rank-sum test (Mann Whitney U test for more than two groups). Non-skewed continuous outcomes were analysed using t-tests (for unadjusted comparisons) and linear regression controlling for treatment group and other demographic and clinical characteristics. Crude and adjusted parameter estimates were calculated with 95% confidence intervals (CI) and p-values. If applicable, a two-sided 95% CI was considered as a default ($\alpha=5\%$). All analyses were conducted using SAS Enterprise Guide 7.13.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and any local regulations. Approvals were obtained from relevant Independent the Ethics Committees and Institutional Review Boards according to local requirements.

Results

Demographics

A total of 372 patients from Belgium (n=42), Italy (n=216), France (n=94), Spain (n=7) and Germany (n=13) were included in the study by 31 sites. Overall, half of the patients included were women (48.7%, n=181) (Table 3). Mean age for the overall patient sample was 37.8 (SD 13.1) years at index date. On average, patients were diagnosed with CD 9.9 (SD 8.9) years prior to the index date. At time of diagnosis an active fistula was reported for 28.5% (n=106) of the patients, mostly anal or perianal fistulas (n=93) followed by combined types (anal or perianal plus either enterovaginal/colovaginal, or enterocutaneous, or enteroenteric/enterocolic) (n=8, 2.2%).

At index date, one third of all patients (38.2%, n=142) had a non-stricturing, non-penetrating with anal/perianal fistula (B1p according to Montreal classification(17)) type of disease behaviour, another third of patients a penetrating with anal/perianal fistula (B3p) type of disease behaviour (36.3%, n=135) and 19.1% (n=71) stricturing with anal/perianal fistula (B2p) type of disease behaviour (Table 2). Anal or perianal fistulas were the most common types (93.6%, n=348) followed by combined types (anal or perianal plus either enterovaginal/colovaginal, or enterocutaneous, or enteroenteric/enterocolic) (n=22, 5.9%). For two patients the type of fistula was not retrievable. For most patients (76.6%, n=285), no extra-intestinal manifestation was reported.

Treatment

The median time between CD diagnosis and occurrence of first reported complex CPF was 5.5 (IQR: 1.0-12.9) years. This period ranged from 0 years to 37.5 years. For most patients (87.4%, n=325) the episode of complex CPF at index date was also their first, whereas for 47 patients (12.6%), at least one complex CPF prior to index date was reported.

Pre-index period

Prior to index date, 5-aminosalicylic acid (5-ASA) was used in 46.2% (n=172) of the patients, steroids in 33.6% (n=125), immunosuppressants in 42.2% (n=157) and anti-TNFs in 48.4% (n=180) as medical treatment for CD, complications) and complex CPFs (Figure 2). The observed CD complications included uveitis, erythema nodosum, aphthous ulcers, and pyoderma gangrenosum.

Table 3. — Sociodemographic and clinical characteristics of patients

	At CD diagnosis (N=372)	At index date (N=372)
Age		
Mean (SD) (years)	27.8 (12.4)	37.8 (13.1)
Median (IQR)	25.0 (19.0, 34.8)	36.0 (27.0, 48.0)
Gender, n (%)		
Female	181 (48.7%)	
Male	191 (51.3%)	
Time from CD diagnosis until index date		
Mean (SD) (years)	9.9 (8.9)	
Median (IQR)	7.3 (2.7, 14.9)	
Length of follow-up period		
Mean (SD) (years)	6.0 (1.0)	
Median (IQR)	6.0 (5.2, 6.9)	
Disease location, n (%)		
Ileal involvement	101 (27.2%)	84 (22.6%)
Colonic involvement	103 (27.7%)	94 (25.3%)
Ileocolonic involvement	144 (38.7%)	135 (36.3%)
Unknown/missing	24 (6.5%)	59 (15.9%)
Upper GI disease		
Yes	15 (4.0%)	11 (3.0%)
No	338 (90.9%)	343 (92.2%)
Unknown/missing	19 (5.1%)	18 (4.8%)
Disease behaviour, n (%)		
Non-stricturing, non-penetrating, without anal/perianal fistula (B1)	116 (31.2%)	0 (0.0%)
Non-stricturing, non-penetrating, with anal/perianal fistula (B1p)	30 (8.1%)	142 (38.2%)
Stricturing, without anal/perianal fistula (B2)	71 (19.1%)	0 (0.0%)
Stricturing, with anal/perianal fistula (B2p)	20 (5.4%)	71 (19.1%)
Penetrating, without anal/perianal fistula (B3)	53 (14.3%)	0 (0.0%)
Penetrating, with anal/perianal fistula (B3p)	42 (11.3%)	135 (36.3%)
Unknown	40 (10.8 %)	24 (6.5%)
Active perianal fistula, n (%)	106 (28.5%)	372 (100.0%)
Type of active perianal fistula, n (%) ^{†‡}		
Anal or perianal	93 (25.0%)	348 (93.6%)
Enterovaginal / colovaginal	1 (0.3%)	0 (0.0%)
Enteroenteric or enterocolic	3 (0.8%)	0 (0.0%)
Combined types [§]	8 (2.2%)	22 (5.9%)
Unknown	1 (0.3%)	2 (0.5%)
Abbreviations: CD = Crohn's Disease; SD = standard deviation; IQR = interquartile range. [†] Percentages were calculated based on total number of patients. [‡] About 60% of complex perianal fistula at index date and during post-index period were trans-sphincteric. [§] Anal or perianal + enterovaginal/colovaginal, anal or perianal + enterocutaneous, anal or perianal + enteroenteric or enterocolic, anal or perianal + enterovaginal/colovaginal + enteroenteric or enterocolic, anal or perianal + enterovaginal/colovesical + enterovaginal/colovaginal + enteroenteric or enterocolic.		

For CD and CD complications at least one surgery for CPF was reported for 41.4% (n=154) of all patients. The most common surgery was partial resection of the small bowel (68.2%, n=105), followed by other surgical interventions (including abscess drainage, ileocolicectomy, ileostomy and ileostomy closure) (18.8%, n=29) and partial colectomy with or without ostomy (16.9%, n=26) (Table 4).

Post-index period

Considering all reported complex CPFs since index date (n=498), most fistulas (61.0%, n=304) were reported as being trans-sphincteric, one fifth as being inter-sphincteric (21.5%, n=107) and 13.1% (n=65) as supra-sphincteric.

Table 4. —Type surgical interventions for CD or complications during the pre-index period by patients

Type of surgical intervention†	Belgium (N=42)	Italy (N=216)	France (N=94)	Spain (N=7)	Germany (N=13)	Overall (N=372)
Partial resection of small bowel +/- ostomy	9 (37.50%)	77 (77.00%)	16 (64.00%)	1 (50.00%)	(66.67%)	105 (68.18%)
Subtotal/total colectomy +/- ostomy	2 (8.33%)	13 (13.00%)	5 (20.00%)	0 (0.00%)	1 (33.33%)	21 (13.64%)
Total colectomy +/- ostomy	3 (12.50%)	3 (3.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (3.90%)
Partial colectomy +/- ostomy	9 (37.50%)	12 (12.00%)	5 (20.00%)	0 (0.00%)	0 (0.00%)	26 (16.88%)
Proctectomy	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Strictureplasty	0 (0.00%)	9 (9.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	9 (5.84%)
Other‡	12 (50.00%)	10 (10.00%)	6 (24.00%)	1 (50.00%)	0 (0.00%)	29 (18.83%)

† One patient could have more than one surgical intervention. ‡ Including abscess drainage (n=11, 37.9% of other surgical interventions), ileocolicostomy, ileostomy and ileostomy closure (n=3, 10.3% each).

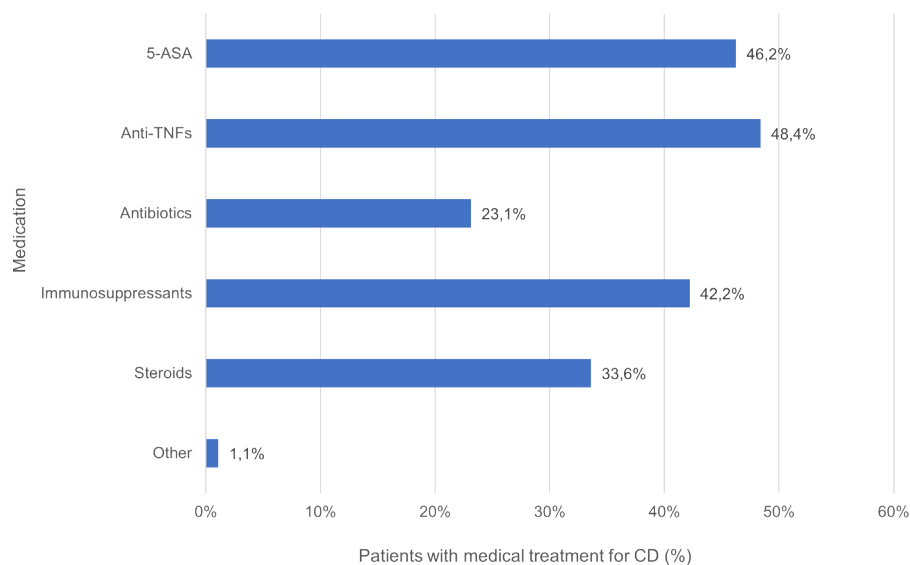


Figure 2. — Percentage of Patients with Medical† Treatment for CD, Complications and CPFs During the Pre-index Period‡. † No distinction was made between monotherapy, combination therapy or both. ‡ Multiple answers were possible.

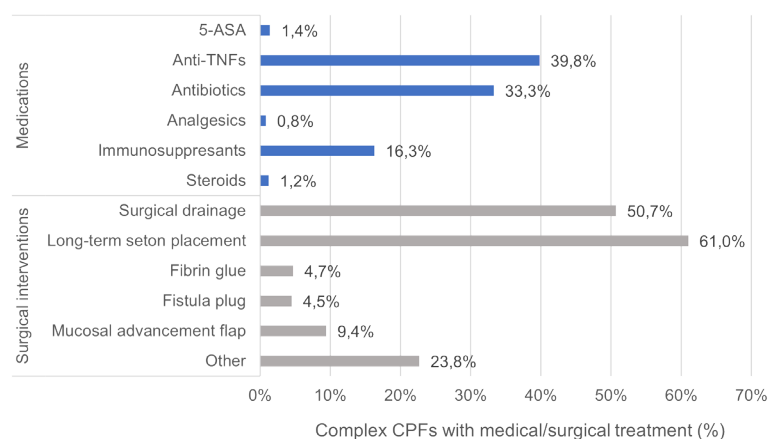


Figure 3. — Percentage of Complex CPFs with Medical† / Surgical Treatment at Index Date and During Post-index Period‡. † No distinction was made between monotherapy, combination therapy or both. ‡ Multiple answers were possible.

At least one medical treatment was provided for 81.5% (N=406) of complex CPFs since index date.

For one third of all complex CPFs, anti-TNFs (39.8%, n=198) and antibiotics (33.3%, n=166) were used for

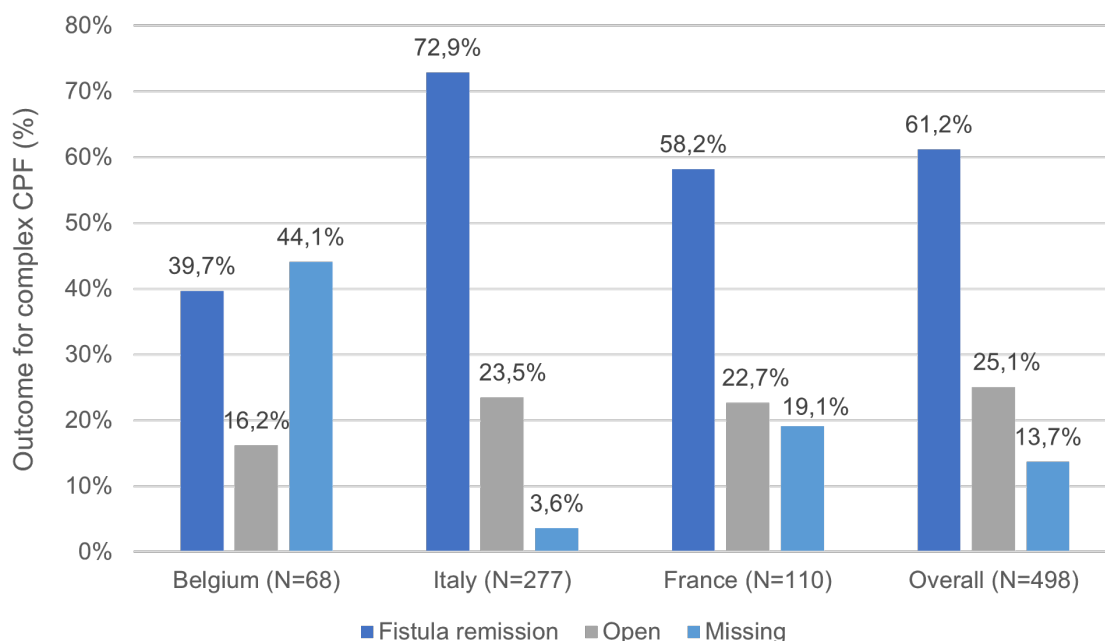


Figure 4. — Outcomes for complex CPF treated between index date and end of data collection based on the last reported fistula drainage assessment[†]. [†]Due to the low sample size, data for Germany and Spain are not shown in this figure.

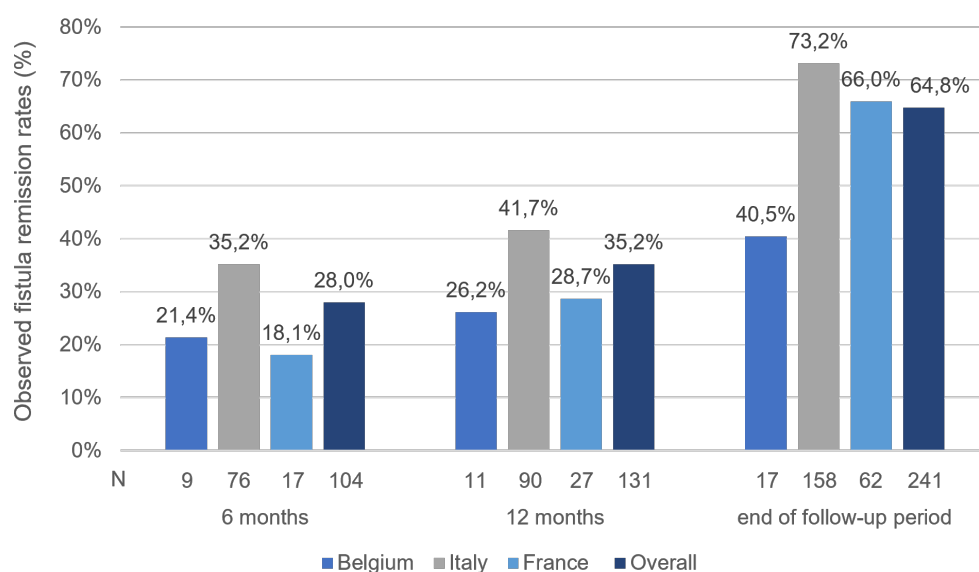


Figure 5 — Fistula remission rates observed corresponding to the complex CPFs treated at index date by patient[†]. [†]Due to the low sample size, data for Germany and Spain are not shown in this figure.

treatment. Immunosuppressants were included in the treatment of 16.3% (n=81) of all CPFs since index date (Figure 3). Most complex CPFs (93.8%, n=467) were treated surgically at least once since index date. The most frequent surgeries were long-term seton placement (61.0%, n=285) and surgical drainage (50.7%, n=237). Other types of surgical interventions were reported for 23.8% (n=111) of the complex CPFs, including fistulotomy (n=38), colostomy (n=5) and ileostomy (n=3) (Figure 3). No data was collected on repairing surgery.

Outcome

The median period from treatment initiation to last fistula drainage assessment used for overall outcome was 2.1 years (IQR: 0.4-4.8 years).

In total, 498 complex CPFs were recorded between index date and end of data collection (median follow-up period 6.0 years), 372 of them at index date and 126 in the follow-up period. Two thirds (61.2%, n=305) of all complex CPFs were reported being in remission based

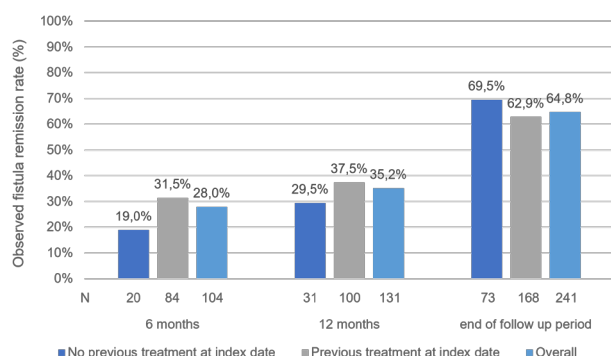


Figure 6. — Fistula remission rates observed corresponding to the CPFs treated at index date (at overall and use of previous treatment which could have influenced outcome of complex CPF at index date) by patient.

on the last reported fistula drainage assessment, whereas 25.1% (n=125) were reported to be open (actively draining). Data was missing for 13.7% (n=68) of all complex CPFs (Figure 4).

The remission rate at patient level for index fistula was 28.0% after 6 months and 35.2% after 12 months. After the entire study follow-up period two thirds (64.8%, n=241) of all patients were reported being in fistula

remission, whereas for 21.8% (n=81) of the patients the last reported fistula drainage assessment was open. Data was missing for 13.4% (n=50) of all patients (Figure 5).

The percentage of patients who were reported as being in fistula remission after 6 months was higher in patients with previous treatment which could have influenced outcome of complex CPFs at index date (31.5%, n=84) than in patients with no previous treatment for complex CPFs at index date (19.0%, n=20). After 12 months, these percentages converge, although the percentage of patients who were reported being in fistula remission was still higher in patients with previous treatment for complex CPFs at index date (37.5%, n=100) than in patients with no previous treatment for complex CPFs at index date (29.5%, n=31) (Figure 6).

A total of 82.7% of patients in fistula remission at 6 months with available data on re-interventions received no re-interventions after index-treatment, 17.3% received 1 or 2 re-interventions. A total of 77.1% of patients in fistula remission at 12 months with available data on re-interventions received no re-interventions after index-treatment, 22.9% received 1 or 2 re-interventions. A total of 58.1% of patients in fistula remission at end of the entire follow-up period with available data on re-interventions received no re-interventions after index

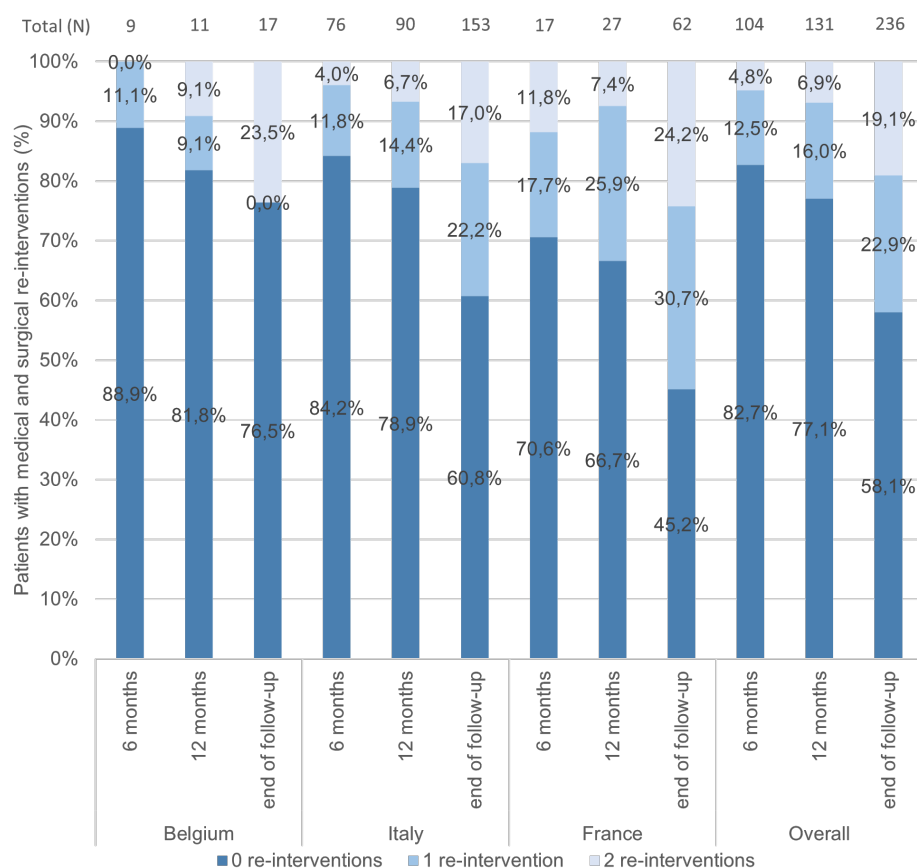


Figure 7. — Percentage of patients with medical and surgical re-interventions of those patients who were in fistula remission at the corresponding timepoints (at 6 and 12 months and at end of the individual follow-up period)†. † Due to the low sample size, data for Germany and Spain are not shown in this figure.

treatment, 42.0% received 1 or 2 re-interventions (Figure 7).

Discussion

This retrospective, multi-national medical chart review study provides a description of the treatment patterns and outcomes of patients with complex CPFs in Belgium, France, Germany, Italy and Spain from 2011 to 2018.

A quarter of patients already had anal or perianal fistulas at CD diagnosis. During the index period and follow-up, a total of 498 complex CPFs were presented. Almost two thirds of these (61%) were trans-sphincteric potentially compromising sphincter function if inadequately treated highlighting the need for optimal therapeutic interventions. Out of the 498 complex CPFs 94% were treated with at least one surgical intervention and 82% with at least one medical treatment.

In our study, long-term seton placement (61%) and surgical drainage (51%) were the surgical interventions most often performed. This is in contrast to two retrospective chart-extraction studies, one of them conducted in the Netherlands and the other one in Spain. The first study extracted data from 232 patients between 1980 and 2000 of whom 78% had complex CPFs. They found that faecal diversion (stoma) (64%) and colectomy (55%), followed by fistulectomy (43%) were the most common surgical interventions in patients with complex CPF (18). The other study published in 2013 conducted in Spain included 313 patients of whom 80% were diagnosed with complex CPF. The study period was not reported. Surgical interventions were reported for 66% of the patients, mostly fistulotomy (37%) and seton placement (32%) (19). According to the ECCO guidelines (2010 and 2016), management of complex CPF includes abscess drainage and seton placement, whereas fistulectomy and fistulotomy should be used thoughtfully due to the risk of incontinence (15, 20). Surgical repairs as generally do not achieve permanent cure, leading to multiple procedures and an increased risk of complications (11,10). A systematic literature review generally found that high proportions of patients experience lack of response or inadequate response to medical and surgical treatment as well as relapse (11).

Based on the ECCO guidelines (15) and considering that the use of anti-TNF has changed significantly since 2000, it was also expected that the vast majority of all complex CPFs in CD patients should be treated with anti-TNF with or without surgical intervention. In the PREFACE study, most of the patients included in the study (90%) were treated with anti-TNFs at some point during the observational period from CD diagnosis until end of follow-up period. However, only about 40% of complex CPFs were treated with anti-TNFs during the (post-)index period which was clearly lower than expected. In the Dutch study mentioned above, mostly immunosuppressants (83%) were used followed by

antibiotics (52%) and anti-TNFs (induction therapy) (51%) in patients with complex CPF (18). Although, it should be considered that the inclusion period for this study started in 1980, before launch of anti-TNF agents. Similarly, in the study conducted in Spain most of the patients received thiopurines (71%), antibiotics (62%) and 54% anti-TNFs (19). The reason for the divergent use compared to the guidelines was not covered by our study and future research on this topic might be necessary for a better understanding. Considering the different study periods of earlier publications and the PREFACE study, the results of the PREFACE study more closely match the treatment recommendations of more recent guidelines valid at time of treatment decisions. Nevertheless, treatment success with anti-TNFs is highly variable with 12-73% of patients with complex CPFs failing on this treatment and with up to 41% of patients with an initial response to anti-TNF treatment relapsing (22). This might be an explanation for the lower anti-TNF treatment rate during the (post-)index period as 48% of the patients had already received anti-TNF treatment in the pre-index period.

Even though a high proportion of fistulas was surgically treated in our study (the majority through drainage with or without seton placement with a low rate for other types of surgery) and more than 80% of them with medical treatment, this treatment achieved fistula remission in only 28% of all patients after 6 months, and 35% of all patients after 12 months based on fistula drainage assessment. Furthermore, the percentage of patients needing medical and surgical re-interventions increased from 17% at 6 months of follow-up to 42% of patients at the end of the entire follow-up period. The high re-intervention rate could be a reason for the relatively high fistula remission rate of 65% of all patients and of 61% of all complex CPFs after the end of the individual study follow-up period. A high re-intervention rate was also found in a recent study by Motamedi et al. published 2021 observing patients with perianal fistula. After a median follow-up period of 23 months, 83% of CD patients had surgical re-interventions after curative surgery and seton placement (23) showing an even higher rate than found in the PREFACE study. These findings are in line with the systematic review in which failure rates of 0-80% (the timepoints of assessment varied between 3 months to a mean of 28 months) and relapse rates of 0-50% (the timepoints of assessment varied between a median of 11 months to a mean of 28 months) were reported for combined medical and surgical treatments (11). In summary, these findings emphasize the need for effective therapies for complex CPFs.

There are clearly some limitations related to the retrospective nature of the study which should be considered for interpretation of results. The use of a retrospective study design to collect information about disease management and outcomes might be associated with a systematic under-recording of information in medical charts. For this study especially the missing information

on treatment outcomes should be considered; fistula drainage assessments were not consistently reported and no information about the duration of the fistula remission was available. Furthermore, the fistula remission rates were not adjusted for any re-interventions. Additionally, a seton was placed in a significant percentage of patients, thus closure and fistula remission, defined as absence of any draining fistulas, could not be achieved. It is worth mentioning that only a low number of patients were enrolled in Spain (n=7) and Germany (n=13). The low numbers of patients from each of these two countries means that the results of these two countries should not be compared to those of other countries. There might be differences in diagnostic and therapeutic protocols for complex CPFs between the different countries which might influence the major outcomes.

Conclusion

There remains an unmet need for safe, effective and targeted treatments that can achieve fistula remission in patients refractory to pharmacological treatment or for whom the only alternative is to pursue surgical interventions that carry the risk of complications and including permanent faecal incontinence. Improved therapeutic strategies and new treatment options are still required to improve outcomes in this debilitating complication of CD.

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Conflicts of Interests

SM, NBE and AFN are employees of Takeda and have Takeda stocks or stock options. MoR is employee of IQVIA. MF has received research grants from AbbVie, Biogen, EG, Janssen, Pfizer, Takeda and Viatrix; consultancy fees from AbbVie, AgomAb Therapeutics, Boehringer-Ingelheim, Celgene, Celltrion, Eli Lilly, Janssen, MRM Health, MSD, Pfizer, Takeda, and Thermo Fisher; and speakers fees from AbbVie, Biogen, Boehringer-Ingelheim, Falk, Ferring, Janssen-Cilag, MSD, Pfizer, Takeda, Truvion Healthcare and Viatrix. LS is a member

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References

1. MAYBERRY JF, LOBO A, FORD AC, THOMAS A. NICE clinical guideline (CG152): the management of Crohn's disease in adults, children and young people. *Aliment Pharmacol Ther* 2013; 37(2):195-203.
2. GOMOLLÓN F, DIGNASS A, ANNESE V, TILG H, VAN ASSCHE G, LINDSAY JO et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017; 11(1):3-25.
3. EGLINTON TW, BARCLAY ML, GEARRY RB, FRIZELLE FA. The spectrum of perianal Crohn's disease in a population-based cohort. *Dis Colon Rectum* 2012; 55(7):773-7.
4. INGLE SB, LOFTUS EV. The natural history of perianal Crohn's disease. *Dig Liver Dis* 2007; 39(10):963-9.
5. FIGG RE, CHURCH JM. Perineal Crohn's disease: an indicator of poor prognosis and potential proctectomy. *Dis Colon Rectum* 2009; 52(4):646-50.
6. COHEN RD, WATERS HC, TANG B, RAHMAN MI. Effects of fistula on healthcare costs and utilization for patients with Crohn's disease treated in a managed care environment. *Inflamm Bowel Dis* 2008; 14(12):1707-14.
7. LICHTENSTEIN GR, YAN S, BALA M, BLANK M, SANDS BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology* 2005; 128(4):862-9.
8. SANDBORN WJ, FAZIO VW, FEAGAN BG, HANAUER SB. AGA technical review on perianal Crohn's disease. *Gastroenterology* 2003; 125(5):1508-30.
9. COLOMBEL J-F, SANDBORN WJ, RUTGEERTS P, ENNS R, HANAUER SB, PANACCIONE R et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; 132(1):52-65.
10. BELL SJ, WILLIAMS AB, WIESEL P, WILKINSON K, COHEN RCG, KAMM MA. The clinical course of fistulating Crohn's disease. *Aliment Pharmacol Ther* 2003; 17(9):1145-51.
11. Panes J, Reinisch W, Rupniewska E, Khan S, Forns J, Khalid JM et al. Burden and outcomes for complex perianal fistulas in Crohn's disease: Systematic review. *World J Gastroenterol* 2018; 24(42):4821-34.
12. Gece KB, Bemelman W, Kamm MA, Stoker J, Khanna R, Ng SC et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut* 2014; 63(9):1381-92.
13. PREFONTAINE E, MACDONALD JK, SUTHERLAND LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2010; (6):CD000545.
14. PEARSON DC, MAY GR, FICK GH, SUTHERLAND LR. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. *Ann Intern Med* 1995; 123(2):132-42.
15. GIONCHETTI P, DIGNASS A, DANESI S, MAGRO DIAS FJ, ROGGER G, LAKATOS PL et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. *J Crohns Colitis* 2017; 11(2):135-49.
16. KELLEY KA, KAUR T, TSIKITIS VL. Perianal Crohn's disease: challenges and solutions. *Clin Exp Gastroenterol* 2017; 10:39-46.

17. SATSANGI J, SILVERBERG MS, VERMEIRE S, COLOMBEL J-F. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; 55(6):749-53.
18. MOLENDIJK I, NUIJ VJAA, VAN DER MEULEN-DE JONG AE, VAN DER WOUDE CJ. Disappointing durable remission rates in complex Crohn's disease fistula. *Inflamm Bowel Dis* 2014; 20(11):2022-8.
19. ARBERAS-DIEZ B, CHAPARRO M, BURGUEÑO P, VERA I, BERMEJO F, MARÍN-JIMÉNEZ I et al. P536 Effectiveness of the available therapeutic options in the treatment of perianal fistulas in patients with Crohn's disease (CD). *Journal of Crohn's and Colitis* 2013; 7:S225.
20. VAN ASSCHE G, DIGNASS A, REINISCH W, VAN DER WOUDE CJ, STURM A, DE VOS M et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis* 2010; 4(1):63-101.
21. WASMANN KA, GROOF EJ DE, STELLINGWERF ME, D'HAENS GR, PONSIOEN CY, GECSE KB et al. Treatment of Perianal Fistulas in Crohn's Disease, Seton Versus Anti-TNF Versus Surgical Closure Following Anti-TNF PISA: A Randomised Controlled Trial. *J Crohns Colitis* 2020; 14(8):1049-56.
22. PANÉS J, GARCÍA-OLMO D, VAN ASSCHE G, COLOMBEL JF, REINISCH W, BAUMGART DC et al. Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease. *Gastroenterology* 2018; 154(5):1334-1342.e4.
23. MOTAMEDI MAK, SERAHATI S, RAJENDRAN L, BROWN CJ, RAVAL MJ, KARIMUDDIN A et al. Long-term outcomes after seton placement for perianal fistulas with and without Crohn's disease. *Colorectal Dis* 2021.