Original Article

Fistula Plug in Fistulising Ano-Perineal Crohn's Disease: a Randomised Controlled Trial

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Abstract

Background and Aims: Anal fistula plug [AFP] is a bioabsorbable bioprosthesis used in ano-perineal fistula treatment. We aimed to assess efficacy and safety of AFP in fistulising ano-perineal Crohn's disease [FAP-CD].

Methods: In a multicentre, open-label, randomised controlled trial we compared seton removal alone [control group] with AFP insertion [AFP group] in 106 Crohn's disease patients with non- or mildly active disease having at least one ano-perineal fistula tract drained for more than 1 month. Patients with abscess [collection ≥ 3 mm on magnetic resonance imaging or recto-vaginal fistulas were excluded. Randomisation was stratified in simple or complex fistulas according to AGA classification. Primary end point was fistula closure at Week 12.

Results: In all, 54 patients were randomised to AFP group [control group 52]. Median fistula duration was 23 [10–53] months. Median Crohn's Disease Activity Index at baseline was 81 [45–135]. Fistula closure at Week 12 was achieved in 31.5% patients in the AFP group and in 23.1 % in the control group (relative risk [RR] stratified on AGA classification: 1.31; 95% confidence interval: 0.59–4.02; p = 0.19). No interaction in treatment effect with complexity stratum was found; 33.3% of patients with complex fistula and 30.8% of patients with simple fistula closed the tracts after AFP, as compared with 15.4% and 25.6% in controls, respectively

[RR of success = 2.17 in complex fistula vs RR = 1.20 in simple fistula; *p* = 0.45]. Concerning safety, at Week 12, 17 patients developed at least one adverse event in the AFP group vs 8 in the controls [*p* = 0.07].

Conclusion: AFP is not more effective than seton removal alone to achieve FAP-CD closure.

1. Introduction

In population-based studies, ano-perineal fistulas occur in approximately 30% of Crohn's disease [CD] patients and are more frequently associated with colorectal involvement.[1,2] They represent a major therapeutic issue and impair quality of life with an increased risk of faecal incontinence,[3] faecal diversion,[4] and late proctectomy.[5] Medications reported to be of benefit in reducing fistula drainage include metronidazole and ciprofloxacin,[6] immunosuppressive agents such as 6-mercaptopurine/azathioprine,[7] cyclosporine,[8] tacrolimus,[9] thalidomide,[10] and most of all anti-tumour necrosis factor α [TNFα] agents.[11] Since Present's publication on infliximab in 1999,[12] anti-TNF agents have changed the paradigm of perianal CD treatment.[13] However, despite this significant progress, anti-TNF agents are incompletely efficacious: only one-fifth of all patients treated completely heal after 1 year of follow-up.[11,14] Moreover, even in cases of closure of draining external orifices after anti-TNF therapy, magnetic resonance imaging [MRI] studies demonstrated that fistula tracks persisted in 73% of cases, which can explain the high risk of recurrent fistulas and abscesses.[15] Therefore, alternative therapies are required.

Surgery remains important in the management fistulising ano-perineal CD [FAP-CD]. Placement of seton drainage is often needed to prevent further abscess formation. Fistulotomy for very low fistulas may also be used; in severe cases and if the rectal mucosa is not ulcerated, sphincter-sparing techniques such as rectal advancement flap, gracilis interposition, or ligation of the intersphincteric tract [LIFT] have been proposed.[16,17,18] In a previous controlled trial of the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif [GETAID], it has been demonstrated that fibrin glue had limited efficacy, with clinical remission in 38% at Week 8 compared with 16% in the control group [*p* < 0.05]. Moreover, the benefit was not significant for patients with complex fistulas, with only 25% achieving closure.[19] More recently, anal fistula plug [AFP] was proposed to achieve closure of fistula tracts. AFP [Surgisis AFP ®] is a collagen bio-prosthetic device made with lyophilised porcine small intestine submucosa. This material has inherent resistance to infection, produces no foreign body or giant cell reaction, and becomes repopulated with host cell tissue, promoting healing processes to obliterate permanently the fistula tract over a period of 3 months.[20] It is supposed that in addition to suturing the plug securely at the primary opening, insertion of a conical plug into the high-pressure area of the fistula produces a mechanically stable system promoting healing. Promising results have been reported in cryptoglandular fistulas, with 83% of efficacy in an open study,[21] and 80% in a non-controlled trial conducted in 30 patients with CD.[22] The aim of the present study was to evaluate efficacy and safety of AFP in the treatment of FAP-CD by a controlled trial.

2. Methods

2.1. Trial design

The present study was a multicentre, open-label, randomised, controlled trial conducted by the GETAID [ClinicalTrials.gov No.2008-A00122-53]. Recruitment took place at 16 sites [14 in France and 2 in Belgium] between June 2008 and December 2011. The institutional Independent Ethics Committee of Paris, France, and of Liège, Belgium, approved the protocol for each participating centre. All patients provided written informed consent before entering the trial. This study was conducted in accordance with the Declaration of Helsinki, in compliance with the consolidated Good Clinical Practice guideline of the International Conference on Harmonisation and with the applicable regulatory requirements.

2.2. Participants

Patients eligible for inclusion into the trial were at least 18 years old and had CD that had been confirmed by endoscopy and histology. The Crohn's Disease Activity Index [CDAI] had to be 250 or less. Patients had at least one active ano-perineal fistula track [between the anus or low rectum and the perineum or vulva] for at least 2 months with seton drainage for at least 1 month. Treatments with azathioprine, 6-mercaptopurine, methotrexate, thalidomide, or anti-TNF were permitted providing the dose was stable for more than 3 months, as well as treatment with aminosalicylates at a stable dose for more than 1 month. Oral corticosteroids were tolerated given at stable dose for at least 2 weeks at equal or less than 15 mg/day equivalent prednisone or 6 mg/day budesonide. Patients were not eligible for inclusion if they fulfilled at least one of the following conditions: anal abscess [defined by collection ≥ 3 mm assessed by MRI within the previous month], recto-vaginal fistula, anal or rectal stricture [if dilation could not allow anal retractor insertion to perform plug suture at the internal opening], anal surgery within the past month, rectovaginal fistula, severe proctitis [ulcerations extending over ≥ 10% of rectal mucosa], corticosteroids > 15 mg/day or budesonide > 6 mg/day, anti-TNF started in the past 6 months or with dose and/or interval modification in the past two administrations, ciclosporin or tacrolimus in the past 3 months, previous use of AFP for FAP-CD, pregnancy, or refusal to receive a porcine device.

2.3. Assignment

Patients were randomly assigned to have either AFP [AFP group] or observation after seton removal [control group]. Randomisation was centralised using permutations tables in a ratio 1:1, stratified both on centre and on stratum, predefined as simple or complex fistula. According to AGA classification, complex fistulas are fistulas with multiple tracts, fistulas with a large ulcer [> 5 mm] at the internal opening, and fistulas with an ano-vaginal tract. The numbers were allocated sequentially in the order of enrolment. Patients could not be included twice in the study. After obtaining informed consent, investigators used a specific form sent by fax, which assigned the eligible patient to the next randomisation number for the centre and stratum concerned.

2.4. AFP group

Either a surgeon or a proctologist carried out the procedure in an operating theatre under aseptic conditions. Enema [Normacol;

Norgine Pharma, France] was administered before the procedure. Broad-spectrum parenteral antibiotic was given on induction of anaesthesia according to French Society of Anaesthesia and Reanimation protocols. The fistula tract was thoroughly rinsed with hydrogen peroxide and saline. All setons were removed during the procedure.

The AFP was hydrated for 2 min in room-temperature saline. When the seton was cut, it was used to pull the plug into the tract. A 2-0 vicryl suture was tied to the tip of the plug, secured to the seton, and the plug was pulled tip first into the internal opening, until resistance was encountered. The excess plug material was trimmed at the level of primary opening, and the plug was buried into the primary opening using a figure-of-eight or X 2-0 vicryl suture, which was inserted deep to the internal sphincter muscle to avoid extrusion of the plug. The head of the plug was optimally covered by at least mucosa and submucosa. Care was taken not to occlude the secondary opening to allow drainage of exudate and to avoid a closed system. In case of multiple fistulous tracks, several plugs could be inserted. All patients were advised to avoid any strenuous activity and to observe sexual abstinence during 2 weeks.

2.5. Control group
Patients in the control group underwent a clinical examination with setons removal without general anaesthesia. At Week 12, AFP was proposed to all patients who did not achieve clinical remission, whatever the treatment they were assigned by randomisation.

2.6. Follow-up and evaluation variables
The medical history with past and current medications was recorded at study baseline. Visits were planned at Weeks 4, 8, and 12 and Months 6 and 12. At each visit, patients underwent a clinical examination without general anaesthesia. For each external opening, draining was assessed on a 5-grade ordinal scale from 0 [no draining] to 4 [passage of stools]. Perianal Disease Activity Index [PDAI][23] was assessed at each visit, and the Inflammatory Bowel Disease Questionnaire [IBDQ][24] was recorded at Week 12 and Month 12. MRI was performed in case of clinical remission between Weeks 12 and 16 and at Month 12.

All primary and secondary end points were *a priori* defined and evaluated by the investigator. The primary end point was clinical remission at Week 12. Clinical remission was defined as the absence of any drainage by all fistula openings occurring spontaneously or after gentle finger compression [grade 0 on the 5-grade scale][23] and the absence of perianal abscess. Patients who did not reach clinical remission, those who did not present at the Week 12 visit, those who experienced severe adverse events, and those who received unauthorised treatments were classified as failures. Secondary end points were clinical remission at Weeks 4 and 8 and Months 6 and 12, and clinical response [at Weeks 4, 8, and 12 and Months 6 and 12] defined as at least 50% of the fistula tracts without any drainage by the external openings and no occurrence of perianal abscess, fistula tract healing at MRI, and tolerance of AFP between inclusion and Month 12. Healing of the fistula tract on MRI was defined according to Van Assche criterias [absence of T2 hyperintensity, absence of cavities/abscesses, and absence of rectal wall involvement].[15]

2.7. Sample size and statistical analysis
The sample size calculation was based on the assumption that AFP would be superior to seton removal alone. A minimum of 102 patients [51/arm] would provide a 90% power to detect a 30% difference in remission rate between AFP and control groups, based on

a two-sided test with type I error of 5%, from the 20% assumed rate of remission in controls.[19] Analysis was made on an intent-to-treat basis. Categorical variables were described globally or per treatment group using frequencies and percentages, and continuous variables were expressed using the median and interquartile range [IQR].

For the primary end point [clinical remission at Week 12], estimation of the effect size was based on stratified relative risk [RR], with the MantelHaenszel test of association. Treatment by strata interaction, that is whether treatment efficacy measured on RR varied across strata or not, was tested using the Breslow and Day homogeneity test. If treatment effect varied across strata [significant interaction between treatment group and stratum], it was planned that complete clinical remission rates would be compared between treatment groups within each stratum. Results were expressed as relative risk [RR] with 95% confidence intervals [95% CIs]. For secondary end points, distributions of scores were compared between treatment groups using the Wilcoxon rank sum test, except for the PDAI whose values over time were compared across randomised arms on the basis of a Poisson regression model with time effect. Chi-square tests or exact Fisher tests were used to compare frequencies of clinical remission, clinical improvement, and ano-perineal abscess. Results were considered significant when the *p* value was less than 0.05. Data were analysed with SAS 9.3 [SAS Inc., Cary, NC] and R 2.15.2 open source [http://www.R-project.org/] software.

2.8. Access to study data
All authors had access to the study data and reviewed and approved the final manuscript.

3. Results
The flowchart diagram of the study is shown in Figure 1. A total of 106 patients with FAP-CD were randomised: 54 patients allocated to the AFP group [including 39 with simple fistula stratum] and 52 patients to the control group [including 39 with simple fistula stratum]. Characteristics of the patients are shown in Table 1. All characteristics were well balanced between the two treatment groups.

3.1. Primary end point
At Week 12, 99 patients were available for evaluation and the remaining 7 were considered as treatment failures. Clinical remission rates were 17/54 [31.5%, 95% CI: 19.5–45.5%] in the AFP group and 12/52 [23.1%, 95% CI: 12.5–36.8%] in the control group [Table 2], [RR stratified on the randomisation strata: 1.31; 95% CI: 0.59–4.02; *p* = 0.19]. No interaction in treatment effect with complexity stratum was found, with fistula closure in 5/15 [33.3%] patients with complex fistula and in 12/39 [30.7%] patients with simple fistula in the AFP group, as compared with 2/13 [15.4%] and 10/39 [25.6%] in controls. In other words, there was no statistical evidence of any heterogeneity in treatment effect, as measured by relative risk of clinical remission in the AFP group compared with the control group [RR = 2.17 in complex fistula, vs RR = 1.20 in simple fistula; *p* = 0.45 by the Breslow-Day homogeneity test]. Finally, there was no evidence of centre effect, though response rates in the AFP arms varied according to the centre from 0 up to 100% vs 0 to 66% in the control arm [Supplementary Figure S1, available as Supplementary data at *ECCO-JCC* online].

Among the 70 patients who did not achieve remission at Week 12, 14/31 and 34/39 initially allocated to the and the seton removal alone groups, respectively, were treated using AFP [Figure 1]. Remission was obtained in 15/48, 12 and 3 in simple and complex
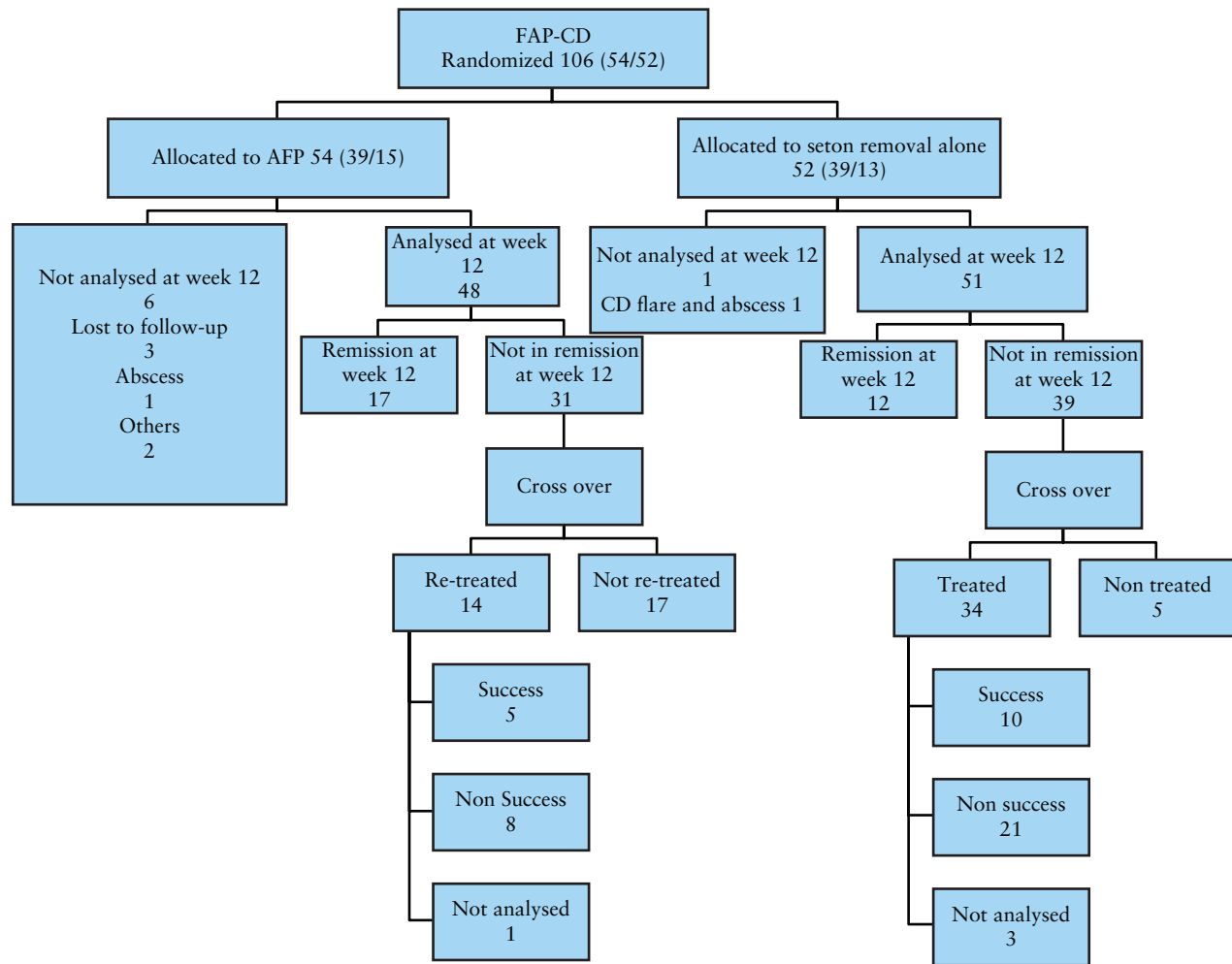
Figure 1. Flow diagram in patients with fistulising ano-perineal Crohn's disease.

fistula, respectively. Among the 54 patients in the AFP group, 22 [40.7%] achieved success after 1 or 2 attempts in 17 and 5 cases, respectively.

3.2. Secondary end points

There was no evidence that clinical remission and clinical response rates differed between the two groups at Weeks 4 and 8 and Months 6 and 12 [Table 2]. The time course of PDAI scores according to randomisation group is displayed in Figure 2. There was no significant difference between groups [$p = 0.38$].

At week 12, MRI was performed in 25 and 20 patients of the AFP and control groups, respectively. Fistula tract healing at MRI was observed in 6/25 [24%] of patients in the AFP group compared with 5/20 [25%] in the control group [$p = 1.00$]. There was no significant difference between groups with regard to the Van Assche or IBDQ scores [Table 2].

Table 3 summarises the main adverse events reported at Week 12 and at the end of the follow-up. At Week 12, 17 patients developed at least one adverse event in the AFP group vs 8 in the control group [$p = 0.07$].

During the whole follow-up, 48 patients experienced 104 adverse events: 27 [50%] in the AFP group and 21 [40%] in the control group had at least one adverse event [including ano-perineal abscesses] [$p = 0.34$]. Main adverse events were: plug avulsion, abscesses, pain, hospitalisation, nausea, diarrhoea, CD flare, and

miscellaneous infection. Anal abscess occurred, respectively, in 11 [20.4%] and 10 [18.5%] patients in the plug and control groups. Plug expulsion occurred in 11 [10.0%] of patients: 6 in the plug group and 5 in the control group.

4. Discussion

The present study, which is the first randomised controlled trial evaluating plug insertion in FAP-CD patients, failed to demonstrate that AFP insertion was more effective than seton removal alone in patients having at least one fistula tract draining for more than 1 month. AFP has been used in the management of anal fistulas, with interesting results reported since 2006. It has been considered as an attractive option in FAP-CD patients where the risk of incontinence associated with fistulotomy contraindicates this procedure. Repopulated with host cell tissue, the AFP is supposed to promote healing processes to obliterate the fistula tract. From a theoretical point of view, this device is a solid bioprosthetic material, less likely than fibrin glue to be expelled from fistula tract. Another presumed advantage of the AFP is that the operative technique requires suturing of the device to the internal anal sphincter at the internal opening, to keep the material in place, allowing time for colonisation with host cells and healing. Since the enthusiastic initial reports were published, several trials have been performed with AFP with more disappointing results. The failure rates found in the

Table 1. Characteristics of the 106 patients with fistulising ano-perineal Crohn's disease at baseline.

	AFP group	Control group
No.	54	52
Age, years*	34 [26; 41]	37 [26; 43]
Female, *n* [%]	36 [67]	32 [62]
Disease duration, years[a]	7 [3; 13]	10 [3; 4]
Current smoker, *n* [%]	23 [43]	16 [31]
Disease location, *n* [%]		
Distal ileum	34 [63]	33 [64]
Proximal ileum, jejunum, stomach	4 [7]	3 [6]
Colon	41 [76]	37 [71]
Rectum	20 [37]	16 [31]
Previous abdominal surgery, *n* [%]	18 [33]	18 [35]
CDAI[a]	79 [41; 138]	86 [48; 134]
Previous fistula surgery, *n* [%]	52 [96]	51 [98]
Fistulotomy	10	8
Fibrin glue injection	14	12
Fistula duration, months[a]	22.5 [10.8; 52.3]	26 [7.8; 52.3]
Type of fistula, *n* [%]		
Simple	39 [72]	39 [75]
Complex	15 [28]	13 [25]
Multiple tract on MRI	7 [13]	6 [12]
Anovaginal tract	0 [0]	0 [0]
Large ulceration at internal opening	2 [4]	4 [8]
PDAI[a]	6 [5; 8]	6 [4; 7.25]
Previous or concomitant medications, *n* [%]		
Corticosteroids	24 [44]	19 [37]
Budesonide	14 [26]	7 [14]
AZA/6 MP	42 [78] / 1 [2]	35 [67] / 3 [6]
MTX	8 [15]	7 [14]
IFX/ADA	38 [70] / 18 [33]	35 [67] / 16 [31]
IBDQ score[a]	167 [136.5; 192]	175 [144.2; 197.2]
Van Assche MRI-based score[a]	9 [4; 13]	10 [4; 12]

[a]Median [IQR].

AFP, anal fistula plug; CDAI, Crohn's Disease Activity Index; PDAI, Perianal Disease Activity Index; AZA/6MP: azathioprine/6-mercaptopurine; MTX, methotrexate; IFX/ADA, infliximab/adalimumab; AFP, anal fistula plug; MRI, magnetic resonance imaging; IBDQ, inflammatory bowel disease questionnaire.

literature for the AFP vary a lot and range from 12% to 87%.[21,22,25,26,27,28,29,30,31,32,33,34,35,36,37] In a systematic review summarising results for CD and non CD anal fistula, O'Riordan *et al.* reported 76 studies or abstracts, and finally retained 20 studies including 530 patients [42 CD patients].[38] The proportion of patients achieving fistula closure varied widely between studies for non-CD, ranging from 0.2 [95% CI: 0.04–0.48] to 0.86 [95% CI: 0.64–0.97]. The pooled proportion of patients achieving fistula closure in patients with non-CD fistulas was 0.54 [95% CI: 0.50–0.59]. The proportion achieving closure in the few CD patients was similar [0.55, 95% CI: 0.39–0.70]. The authors concluded that AFP had not been adequately evaluated in the CD population. Only two randomised controlled studies have been published for AFP in non-CD fistulas. They compared AFP with mucosal advancement flap.[39,40] In the first study, a large number of recurrences in the fistula plug group led to premature closure of the trial.[39] The second study, which included 60 patients with a follow-up of 11 months, showed a recurrence rate of 71% and 52% in the AFP group and the mucosal advancement flap group, respectively (not statistically significant).[40]

Table 2. Response rates in 106 patients with fistulising ano-perineal Crohn's disease.

	AFP group	Control group	*p*-value
	n = 54 *n* [%]; median [IQR]	*n* = 52 *n* [%]; median [IQR]	
Clinical remission			
W4	16 [29.6]	19 [36.6]	0.67
W8	16 [29.6]	15 [28.8]	0.82
M6	19 [35.2]	16 [30.8]	0.24
M12	15 [27.8]	12 [23.1]	0.43
Clinical response			
W4	10 [18.5]	5 [9.6]	0.27
W8	8 [14.8]	4 [7.7]	0.36
M6	2 [3.7]	6 [11.5]	0.16
M12	4 [7.4]	3 [5.8]	1.00
PDAI score			
W4	4 [3; 7]	4 [3; 6]	0.38[a]
W8	4 [3; 7]	5 [3; 7]	
W12	4 [3; 7]	5 [3; 7]	
M6	3 [2; 4]	3 [2.25; 4]	
M12	3 [2; 4]	5 [2.5; 6.5]	
Van Assche MRI score			
W12	6 [4; 10]	8 [3; 12]	0.63
M12	3 [1; 7.5]	3 [1; 7.5]	0.97
IBDQ score			
W12	182 [128; 195.5]	174.5 [138; 192]	0.96
M12	194 [173; 198.5]	187 [166; 194]	0.62

AFP, anal fistula plug; PDAI, Perianal Disease Activity Index; MRI, magnetic resonance imaging, IQR, interquartile range; IBDQ, inflammatory bowel disease questionnaire.

[a]Based on a Poisson regression model incorporating time.

The present controlled trial did not confirm those preliminary promising results. Among the hypotheses to explain such results, smouldering sepsis is not relevant as patients had had MRI within the past month before inclusion and were excluded if a collection ≥ 3 mm was assessed by this examination. Several other explanations may be provided. First, we may wonder if variables such as operative technique or perioperative care could influence the probability of success or failure associated with the AFP. The plug extrusion is a complication felt by many to be a 'learning curve issue' for the surgeon. However, surgeons in our study were experienced in anal fistula surgery; all plugs were inserted according to the guidelines presented in a previous consensus meeting.[41] The dislodgement rate was 10%, a proportion comparable to the literature's rates of 8.7% reported in O'Riordan's review.[42] Second, we may have included particularly refractory disease. Part of our patients had persistent ano-perineal fistulas while they were treated with biologicals and, for the majority, on immunosuppressant therapy. Many had had a previous attempt to close their fistulas, including with fibrin glue injection. We also observed a high rate of abscesses that occurred in 11 and 10 patients in the plug and control groups, respectively. For comparison, in our previous trial with fibrin glue, only one abscess occurred in the control group.[19]

Finally, our study has some limitations. First, the sample size was computed in order to detect a large difference in response rate, from 20% in the control up to 50% in the AFP arm. Actually, fistula closure at Week 12 was achieved in 31.5% in the AFP group vs 23% in the control group, and this exemplifies the over-optimistic assumed effect of AFP when the trial was scheduled. Of note, the
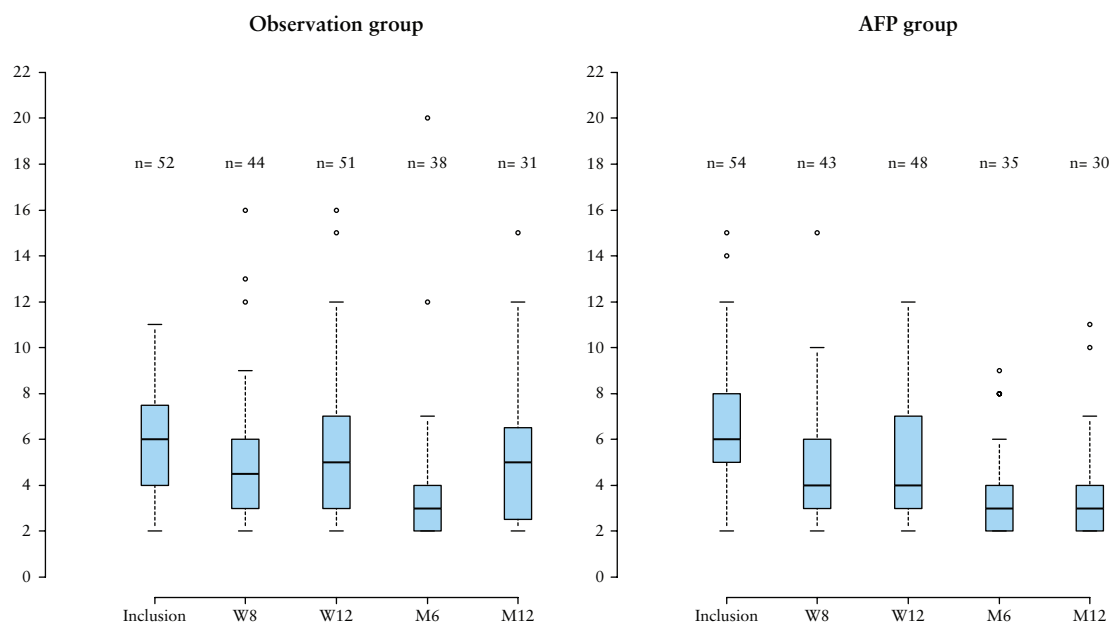
Observation group   **AFP group**

Figure 2. PDAI score evolution according to time and randomisation in 106 patients with fistulising ano-perineal Crohn's disease. PDAI, Perianal Disease Activity Index; AFP: anal fistula plug.

Table 3. Adverse events according to treatment between inclusion and primary end point [Week 12] and after 1 year of follow-up in 106 patients with fistulising ano-perineal Crohn's disease.

	AFP group [*n* = 54]	Control group [*n* = 52]
At week 12		
No. of adverse events [No. of patients]	25 [17]	11 [8]
Abscesses	6 [4]	4 [4]
Plug avulsions	5 [5]	0
CD flare	1 [1]	0
Abdominal pain	1 [1]	0
Miscellaneous	12 [6]	7 [4]
After 1 year of follow-up		
No. of adverse events [no. of patients]	56 [27]	48 [21]
Abscesses	20 [11]	13 [10]
Plug avulsions	8 [6]	5 [5]
CD flare	2 [2]	5 [4]
Abdominal pain	2 [2]	3 [3]
Miscellaneous	24	22

AFP, anal fistula plug; CD, Crohn's disease.

response rate varied across centres, illustrating that such a surgical procedure may be difficult to apply. Our study was not blinded, as the investigator performed the end point evaluation, which could have induced bias. The primary end point of 12 weeks could be considered as a relatively short follow-up. However, we chose this end point because in our previous trial we demonstrated efficacy of fibrin glue at Week 8 in FAP-CD, which is an even shorter period.[19] Finally, although there was no statistical evidence of any heterogeneity in treatment effect, the potential interest of the AFP could be increased in cases of complex fistula, so that further trials should focus on such a population.

To conclude, AFP should not be considered for ano-perineal fistulas] closure in CD as it is not more effective than seton removal alone. Other procedures should be proposed, such as fibrin glue injection especially in single fistula, or mucosal advancement flap in single or complex fistulas, even if they have limited efficacy. New techniques like stem cells injections[43,44] or ligation of the intersphincteric tract,[45] that are still under evaluation, should be assessed by adequate randomised controlled studies.

Conflict of Interest

G. Bouguen has received fees for lectures from MSD, Ferring and Abbvie.
E. Louis has received fees for: educational grant, MSD, Abbvie; speaker fees: Abbvie, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen; advisory board: Abbvie, Ferring, MSD, Takeda, Mitsubishi Pharma, Celltrion.
X. Hébuterne received funding from: Abbvie, Fresenius Kabi and Takeda, for advisory activity, as a member on an advisory board; and from Abbvie, Arard, Ferring, Fresenius Kabi, Mayoli-Spindler, MSD, Nestlé, Norgine, Nutricia, and Takeda, for educational activities.
G. Savoye received: lecture fees from Vifor, HAC Pharma, Abbvie, MSD, and Ferring France; travel grant from Ferring, Abbvie, and MSD France; research grant from Ferring.
D. Laharie has received fees for lectures and boards from AbbVie, MSD, Janssen, Takeda.
Y. Bouhnik has received: fees for consultancies from BMS, Shire, Sanofi, Norgine Pharma, MSD, Abbvie, Astra Zeneca, Roche, and Takeda Millenium; stock ownership from Inception IBD, San Diego, CA, USA; honoraria from BMS, MSD, Abbvie, Teva, Ferring, Vifor Pharma, HAC, Mayoli-Spindler; paid expert testimony from Abbvie; travel grants from Abbvie, MSD, Ferring, Takeda.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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